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ORIGINAL RESEARCH ARTICLE

Second primary cancer prevalence in differentiated thyroid cancer patients and correlation with thyroid primary tumor stage: A population-based cohort study in Iran

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ABSTRACT

Introduction: Thyroid cancer is the most common endocrine malignancy. This often involves the middle-aged and active population, typically younger compared to those with other types of cancers. Some people with thyroid cancer may develop secondary malignancy. The reason for this is not well understood. This study was designed to evaluate the prevalence of second primary cancers in patients with differentiated thyroid cancer and its probable relationship with the severity of treatment and staging of the primary tumor.

Methods: Among 2638 patients who underwent thyroidectomy between 1996 and 2018, we checked cases who suffered from non-thyroidal second primary cancers before, during, or after the diagnosis of thyroid cancer. Forty-nine patients met the criteria and were included in the study. The information was gathered from the medical records and supplemented by direct communication with the patients. The Data was then analyzed using appropriate statistical test with SPSS version 22, considering a p-value of 0.05 was considered as significant.

Results: Out of the 2638 checked records reviewed, 49 patients (1.85%) were found to have second primary cancers with 75.5% being female. One patient had two concurrent second primary cancers, while the remaining 48 patients had a single second primary cancer. Most of the thyroid cancers were papillary (89.8%, 44 cases), with the others remaining cases being follicular type. Stage 2, according to the 8th AJCC staging system, was the most common (50%), followed by stage 1 (36.8%) among the primary staging categories. Breast cancer was the most prevalent (17 cases), followed by hematologic malignancies (8 cases) and GI tract cancers (8 cases).

Conclusion: The findings revealed a significant increase in the number of breast cancers in patients with the differentiated thyroid cancer (DTC), which was not observed for other malignancies.

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INTRODUCTION

Thyroid cancer is the most common endocrine malignancy and its global incidence has significantly increased over the past three decades [1]. According to cancer statistics, thyroid cancer ranks fourth in term of incidence rate [2]. This type of cancer is more prevalent in women, with ratio of of 3:1 compared to the men in most of the world [1, 3]. It is primarily prevalent in middle-aged people with the median age for diagnosis for diagnosis being around 51 years old and nearly half of the cases occurring between 45 and 64 years old [1]. A recent retrospective study conducted on 631 thyroid cancer patients revealed the risk factor for recurrence and mortality include being female, diagnosis at an age over 45, tumor size and distant metastasis [4]. Differentiated thyroid cancer (DTC) is the most prevalent thyroid malignancy arising from follicular thyroid cells. IT includes papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), and Hurthle cell cancer with PTC being the most prevalent subtype (90%).

The presence of oncogenes, radioactive treatment or exposure to ionizing radiation may lead to different cancers [5]. Management of thyroid cancer treatment includes surgery and the use of radioiodine (I-131) therapy [6]. Radioiodine is primarily excreted through the urinary system. Moreover, radioiodine is excreted in the gastrointestinal and salivary glands. A second primary malignancy may be a long-term complication of radioactive iodine treatment for thyroid carcinoma [7, 8]. Subsequent development of malignancy following any radiation exposure is well recognized and is the a potential risk for radioiodine therapy [9]. In some situations, external beam radiotherapy has a role in thyroid cancer treatment [10]. It is important to carefully weigh the risk and benefits of treatments with radiation exposure as far as the possibility of second primary malignancy is concerned [9].

In a noticeable group, second primary malignancies occur concurrently or even before thyroid cancer, when the radiation exposure and/or iodine treatment do not justify the reason [11]. Another proposed theory for the second primary cancer is the presence of shared genetic factors such as BRAF mutations, which increase the risk of breast cancer, colorectal cancer, non-small cell lung cancer, melanoma, and head and neck cancers [12]. As well, RAS activation is related to spontaneous thyroid cancer [13]. Furthermore, the RET mutation is more common in thyroid cancers caused by radiation [14]. Some studies have also shown a relationship between breast cancer and thyroid cancer. As mentioned earlier, sporadic thyroid cancer is more common in women and may be caused by estrogen receptors in the thyroid. On the other hand, some researchers have attributed the increase in the incidence of breast cancer after radioactive iodine treatment to the presence of Na-I transporters in the glandular tissue of the breast [8].

A study by Berthe et al. [15] showed that women with DTC are at risk for second primary cancer development. It had been shown that the second primary malignancy was related to the presence of DTC but not to low and medium cumulative doses of radioiodine [16]. In a cohort study of patients with thyroid cancer, the most common secondary cancer in women was breast cancer, as was prostate cancer in men. Patients who were treated with radioiodine had a higher risk of developing salivary gland cancer [11]. Another study discovered that 7.2% of patients had non-thyroidal second primary cancers (NTSPCs), the most common of which was breast cancer. In addition, a higher risk of developing thyroid cancer is related to patients who were previously treated for head and neck cancers (such as lung, salivary gland, esophageal, and larynx cancers) [17].

Considering that the etiology and prevalence of second primary cancers among thyroid cancer patients are not yet well understood, we decided to assess the prevalence of second primary cancers in our DTC patient population and possible correlations with thyroid disease pathology, primary staging, and treatment modalities.

METHODS

Patients

A retrospective single-center study was conducted on a large group of DTC patients at our institution. We carefully analyzed the data of 2638 DTC patients who were referred to our department after thyroidectomy and were treated and followed up routinely between the years 1995 and 2020 among them we detected 49 patients who had a second primary cancer. Thorough background data, including gender, past medical histories like Hashimoto thyroiditis, head and neck radiation and any family history of thyroid cancer, were recorded. Surgical, anatomical-pathological, and clinical data of tumors (for example, type and pathologic

subtype, TNM staging according to the 8th AJCC, extra-thyroid invasion, and tumoral focus numbers) were retrieved from clinical records. The cumulative dose of administered radioiodine, as well as possibly performed neck EBRT or IMRT, and the dosage, were all recorded. If required, the patients were again contacted for follow-up and update of clinical data. Patients gave their informed consent to the use of their data for research purposes, and the study was approved by the ethical committee of Mashhad University of Medical Sciences (code number: IR.MUMS.MEDICAL.REC.1398.109).

DTC treatment modalities and follow-up

Data on treatment modalities included type of treatment, type of surgery, basic serum thyroglobulin and anti-thyroglobulin level, number of radioiodine treatment, and cumulative radioiodine therapy. All patients underwent surgical treatment (i.e., total or near-total thyroidectomy with lymphadenectomy only if lymph node metastases were found before surgery). Subsequently, patients' responses to therapy, follow-up duration time, one-year response to treatment (according to ATA guidelines), last follow-up visit and time of the best response to treatment were recorded. According to a standard protocol of that time, most of the patients received radioiodine treatment for thyroid remnant ablation after levothyroxine withdrawal.

Finally, information concerning the second primary cancers namely time of occurrence, type of thyroid cancer, history of chemotherapy and radiotherapy for the second primary were obtained.

Statistical analysis

The statistical analysis was performed using the 22.0 SPSS statistical package. A *p*-value of less than 0.05 was considered statistically significant. Pearson's chi-squared test was used to evaluate differences in counts and frequencies between groups for categorical variables. In contrast, the Student's *t*-test was used to assess differences between groups for continuous variables. The Kaplan-Meier "time-to-event" method was used to generate curves of cumulative incidence of NTSPC among classes of I-131 dose. The risk of NTSPC in patients with thyroidal cancer diagnosed before and after DTC was estimated using the standardized incidence rate (SIR), which is a ratio of an observed to an expected number of patients with NTSPCs.

RESULTS

Descriptive analysis of the study group

Among the 2638 DTC patients included in the study, 49 had a second primary cancer; of these, the most common DTC type was PTC (Figure 1), and the most common subtype was classic (Figure 2). Among these, 37 were female (75.5%) and 12 were male (24.5%). The mean age at DTC diagnosis was 49.94±14.91 years (median 41; range 5-81 years).

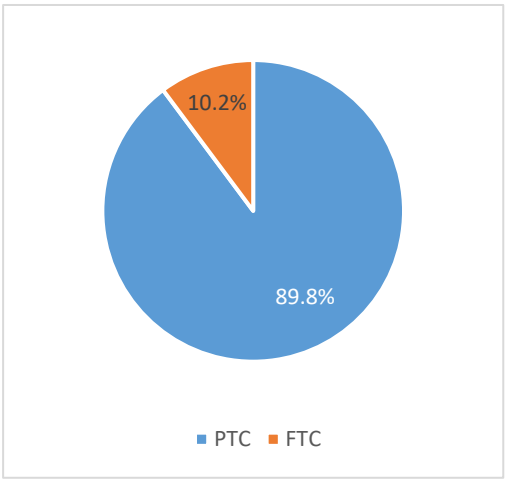

Figure 1. Differentiated thyroid cancers (DTC) diagnosed by pathology (PTC: Papillary thyroid carcinoma, FTC: Follicular thyroid carcinoma)

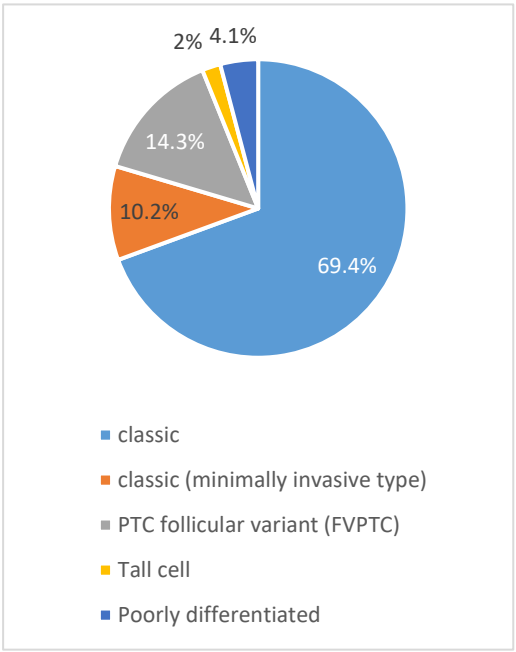

Figure 2. Different differentiated thyroid cancers (DTC) subtypes

A total of 50 NTSPCs (non-thyroidal second primary cancer) were observed in 49.2638 patients in our study group (1.85%; Group I), while in the other 2589 patients (98.15%; Group II), no NTSPC was observed. The demographic and clinical characteristics of both groups are reported (Table 1). In group 1, mean age was higher than that of Group 2 (49.94 ± 14.91 vs. 41.5 ± 14.7). By the time of the study, unfortunately eight patients in group 1 passed away (16.3%); 2 cases succumbed to advanced NTSPCs, 3 cases to diffuse metastatic thyroid cancer, and one patient to non-cancer etiology. In two cases, the differentiation of DTC and NTSPC as the cause of death was impossible.

We asked patients for family history of DTC, personal history of childhood Tinea Capitis, possibly treated with radiation, history of head and neck radiotherapy, and history of Hashimoto thyroiditis. Seven patients (14.3%) had a history of head and neck radiotherapy before the diagnosis of DTC.

There was a significant relationship between history of radiation therapy to the head and neck and the occurrence of second primary malignancy. Also, a significant relationship was observed between history of tinea capitis which was mainly treated by low dose radiation to the scalp and the incidence of second primary malignancy (Table 1).

We observed 24.49 NTSPCs in 24 patients diagnosed before DTC (the pre-DTC group) and 11.49 NTSPCs in 11 patients diagnosed after DTC (the post-DTC group). The apparent discrepancy in the total number of patients and malignancies occurs because one patient developed two NTSPCs (one before and the other one after DTC). In contrast, ten patients developed a second malignancy during the diagnosis process of DTC (concurrent diagnosis) (Table 2).

Table 1. Past medical and past family histories of two groups

History	Group 1 n[%]	Group 2 n[%]	Odds ratio	p-value	CI[2.5%]OR	CI[97.5%]OR
Family history of thyroid cancer	2 [4.1]	106 [6]	0.59	0.7200	0.06	3.01
History of Tinea Capitis in childhood treated with radiation	4 [8.2]	20 [1.1]	25.11	0.0001	3.15	1122.35
History of Hashimoto thyroiditis	4 [8.2]	274 [15.6]	0.45	0.2300	0.10	1.44
History of head and neck radiation	7 [14.3]	25 [1.4]	14.67	0.0060	1.55	698.97

Table 2. The time interval between differentiated thyroid cancer (DTC) and non-thyroidal second primary cancers (NTSPCs) diagnosis

NTSPCs diagnosis	Number [%]
Pre-DTC	24 [52.5]
Concurrent with DTC	10 [21.7]
Post-DTC	11 [23.9]
Pre- and post-DTC	1 [2.2]
Total	45 [100]

The most frequent tumors observed were breast cancer and gynecologic/urologic tumors in the post-DTC group and breast cancer and gynecologic tumors in the pre-DTC group (Table 3).

To evaluate the correlation between the diagnosis of NTSPC and I-131 treatment, we excluded the 17 NTSPCs diagnosed before DTC. The correlation between NTSPC and clinicopathological features and radioiodine treatment was also investigated (Table 4).

In the next step, the comparison of the past radiotherapy state and NTSPCs earliness or lateness showed a p-value of more than 0.05 (Table 5).

In the last step, we compared the timeframe for diagnosing metachronous cancers (Table 6).

Table 3. Type of non-thyroidal second primary cancers (NTSPCs) and time of occurrence

Cancer type	Status	Time of NTSPC diagnosis [percent]		p-value
		Pre-DTC	Post-DTC	
Urologic	Yes	0 [0%]	3 [100%]	0.025
	No	24 [75.0%]	8 [25.0%]	
	Total	24 [68.6%]	11 [31.4%]	
Breast	Yes	10 [71.4%]	4 [28.6%]	0.999
	No	14 [66.7%]	7 [33.3%]	
	Total	24 [68.6]	11 [31.4%]	
Hematologic	Yes	4 [66.7%]	2 [33.3%]	0.999
	No	20 [69.0%]	9 [31.0%]	
	Total	24 68.6%]	11 [31.4%]	
Neurologic	Yes	4 [100%]	0 [0%]	0.285
	No	20 [64.5%]	11 [35.5%]	
	Total	24 [68.6%]	11 [31.4%]	
Dermatologic	Yes	3 [100%]	0 [0%]	0.536
	No	21 [65.6%]	11 [34.3%]	
	Total	24 [68.5%]	11 [31.4%]	
ENT	Yes	1 [100%]	0 [0%]	0.999
	No	23 [67.6%]	11 [32.4%]	
	Total	24 [68.5%]	11 [31.4%]	
GI tract	Yes	2 [50%]	2 [50%]	0.575
	No	22 [71.0%]	9 [29.0%]	
	Total	24 [68.6%]	11 [31.4%]	
Gynecologic	Yes	11 [73.3%]	4 [26.7%]	0.721
	No	13 [65.0%]	7 [35.0%]	
	Total	24 [68.6%]	11 [31.4%]	

DTC: Differentiated thyroid cancer

Table 4. Non-thyroidal second primary cancers (NTSPCs) and radioiodine cumulative dose

Cancer	Number	Average radioiodine cumulative dose	p-value
Urologic	4	268.75 ± 146.31	0.151
Breast	15	259.85 ± 166.67	0.578
Hematologic	8	122.93 ± 113.75	0.748
Neurologic	5	247.02 ± 168.00	0.738
Dermatologic	6	81.67 ± 79.35	0.210
ENT	2	21.21 ± 15.00	0.066
GI tract	8	162.81 ± 146.88	0.758
Gynecologic	17	253.39 ± 170.59	0.503

Table 5. Radiotherapy and non-thyroidal second primary cancers (NTSPCs) state

Past radiotherapy history	Pre-DTC	Post-DTC	p-value
Yes	2 [8.3%]	1 [9.1%]	0.999
No	22 [91.7%]	10 [90.9%]	
Total	24 [100%]	11 [100%]	

DTC: Differentiated thyroid cancer

Table 6. Mean time between non-thyroidal second primary cancers (NTSPCs) diagnosis and differentiated thyroid cancer (DTC) diagnosis

Cancer	Status	Number	Mean duration between DTC and NTSPCs ± SD [years]	p-value
Urologic cancers	Yes	4	27.1±88.1	0.85
	No	36	18.4±72.6	
Breast cancer	Yes	12	84.6±25.9	0.15
	No	28	62.2±43.4	
Hematologic malignancies	Yes	6	7.6±15.7	0.37
	No	34	50.3±35.6	
Neurologic cancers	Yes	4	8.4±15.5	0.95
	No	36	87.3±64.6	
Skin cancers	Yes	6	75.0±64.1	0.19
	No	34	44.4±83.6	
ENT-related cancers	Yes	1	98.3±51.6	0.59
	No	39	42.0	
GI cancers	Yes	6	85.1±6.3	0.40
	No	34	25.4±84.6	
Gynecologic cancers	Yes	13	31.6±5.9	0.20
	No	27	71.2±49.4	

DISCUSSION

In this study, we found that 49 patients developed 50 secondary cancers. Out of these, eight patients passed away (16.3%), 2 from NTSPC, three from metastatic thyroid cancers, and one from non-cancer causes. It was impossible to distinguish between advanced thyroid cancer and other malignancy as the leading cause of death for two patients.

We found that 89.8% (44 patients) had PTC, and five patients suffered from FTC. The most common subtype was classic (69.4%), and most patients were in stages 1 (36.8%) and 2 (50%). All of the patients underwent thyroidectomy, with most receiving total thyroidectomies (87.8%).

The treatment of 84.4% of patients was classic (total thyroidectomy and receiving an ablative dose of radioactive iodine during the first six months after surgery). Radioactive iodine therapy was performed only once in most patients (61.2%), and the mean cumulative dose was 201.98±147.86 mCi. In the follow-up period, three patients needed re-operation for treatment of recurrence or gross residual tissues, and five patients underwent neck radiotherapy.

One patient had three malignancies: a pre-DTC second malignancy, a DTC, and a post-DTC second malignancy. In others, 52.5% of cancers were detected pre-DTC. The average time between DTC and NTSPC was 6.45±3.89 years. This time was not significantly different between pre-DTC and post-DTC second primary cancer diagnoses.

Approximately one-quarter of patients underwent radiotherapy, of which 39% were for treatment of NTSPC. As is known, radiotherapy is not a significant risk factor. However, the radiotherapy site, the type of NTSPC, and the interval time between RT and NTSPC are essential. A group of patients (14.6%) received radiotherapy to treat both DTC and NTSPC. A considerable number of patients (65.9%) had chemotherapy courses for treatment of NTSPC; that was not significantly correlated with the earliness or lateness of DTC. Also, the history of radiotherapy for the treatment of DTC was not significantly correlated with NTSPC development.

The most prevalent second primary malignancies were gynecologic (including breast cancer) [17], hematologic [8], and GI tract-related [8]. The most common type was breast cancer [15].

Urologic cancers were significantly increased after diagnosis and treatment of DTC, but this was not true for other NTSPCs. The mean age of patients with urologic cancers and DTC and patients who had DTC and non-urologic NTSPC was similar.

Finally, our study showed that the average cumulative dose of radioactive iodine was the same among those who were suffering from NTSPC and those who were not suffering from second cancers; thus, we cannot consider RAI as a risk factor for NTSCPs.

Fallahi et al. studied the relationship between iodine cumulative dose and NTSPC in 973 patients. They found a cumulative dose of more than 40 GB, correlates to increased occurrence of NTSPC [18]. Piciu et al. found different results in 2016. They concluded that the increased risk of malignancies like uterine, ovarian, and breast cancer is not dependent on cumulative doses of radioactive iodine but on the occurrence of DTC itself [16]. In our study, we found that the

occurrence of NTSPC is not related to the cumulative dose of radioactive iodine. Moreover, we found that gynecologic cancers (e.g., breast cancer) are not significantly increased after DTC, but urologic cancers are significantly increased after treatment of thyroid cancers.

Izkhakov et al. studied 11538 patients with DTC over 30 years. They found that 1032 patients had NTSPCs, of which most were breast and prostate cancers. In that study, patients who received radioactive iodine therapy developed more salivary gland cancers [11]. The results of the study of Rubino et al. were similar. Among the 39000 patients with DTC, 2821 got NTSPC; that most commonly was breast cancer [17]. In our study, the most common cancer was breast cancer, too. However, none of the studied patients suffered from salivary gland cancer. There was no significant relationship between radioactive iodine cumulative dose and NTSPC occurrence after treatment of DTC.

Berthe et al. found 58 cases of solid cancer (NTSPC) among 875 cases of DTC. This was 1.3 times more for males and 1.5 times more for females than in a healthy population. They found occurrence of urologic cancers in females are significantly related to DTC [15]. Our study results were similar; however, we found a higher occurrence of urologic cancer frequently after DTC treatment in the entire population, not just in females.

Cappagli et al. investigated 101 cases of NTSPCs among 1096 cases of DTCs, which predominantly occurred post-DTC. The majority of NTSPCs were breast and urologic cancers. Nevertheless, the occurrence of breast and hematologic malignancies before DTC was more dominant. They found that the mean time between radioactive iodine therapy and NTSPC was 10.52±7.69 years. The occurrence of NTSPC was not related to the cumulative radioactive iodide dose. And NTSPCs occurrence was similar to that of a healthy population [19]. In our study, breast cancer was the most common NTSPC and urologic cancers significantly increased after DTC. We investigated the interval time of DTC diagnosis and NTSPC (instead of I-131 therapy and NTSPC), which was 6.45±3.89 years, considerably different from that study.

Previous investigations has demonstrated that estrogen receptor-positive breast cancers are more likely to be associated with thyroid cancers [20, 21], even though this is not true for triple negative breast cancers [20]. On the other hand, patients with thyroid cancers are less likely to have estrogen-receptor positive breast cancers [21].

We also categorized the TNM staging data of DTC patients by AJCC versions 7 and 8. Considering the N status, N1 was more common than N0 (by TNM7: N1a 36.7% and N1b 18.4%; according to TNM8: N1a 20.4% and N1b 34.7%), and most of the patients (63.3%) were in the M0 stage for metastasis. In addition, we evaluated response to treatment in patients one year after the operation and radioiodine therapy. One-year responses to treatment in 29.6% of cases were excellent, and in 61.5% of cases, the last-visit response was excellent.

Limitation

The study was retrospective in nature and the medical record were incomplete and not desirable. We made our best to address these shortcomings. Additionally, in some cases, the patients expired, and it was challenging to gain more information.

Lastly, in this cross-sectional study, we were unable to establish a cause-and-effect relationship or determine the risk factors of cases; we only examined the statistical relationship.

CONCLUSION

Most of the second-primary malignancies were gynecologic cancers, followed by hematologic and GI tract malignancies. The most common cancer was breast cancer. The cumulative iodine dose was statistically similar between the group of patients who had non-thyroidal second primary and the group who did not have any second primary malignancies. According to our data, the incidence of urologic malignancies significantly increased after the diagnosis of DTC, and this relationship was not observed for other cancers.

REFERENCES

1. Seib CD, Sosa JA. Evolving understanding of the epidemiology of thyroid cancer. Endocrinol Metab Clin North Am. 2019 Mar;48(1):23-35.
2. Kong N, Xu Q, Zhang Z, Cui A, Tan S, Bai N. Age Influences the prognosis of anaplastic thyroid cancer patients. Front Endocrinol (Lausanne). 2021 Jul 27;12:704596.
3. Rahbari R, Zhang L, Kebebew E. Thyroid cancer gender disparity. Future Oncology. 2010;6(11):1771-9.
4. Karimi N, Faradmal J, Zakavi SR, Roshanaei G, Naderi A. Assessment of risk factors on the relapse and death in patients with thyroid cancer in Khorasan Razavi province, during 2005-2015. J Inflamm Dis. 2019;23(2):128-39.
5. Williams D. Radiation carcinogenesis: lessons from Chernobyl. Oncogene. 2008 Dec;27 Suppl 2:S9-18.

6. Schlumberger M, Leboulleux S. Current practice in patients with differentiated thyroid cancer. Nat Rev Endocrinol. 2021 Mar;17(3):176-88.
7. Lee SL. Complications of radioactive iodine treatment of thyroid carcinoma. J Natl Compr Canc Netw. 2010 Nov;8(11):1277-86.
8. Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scélo G, Pukkala E, Hemminki K, Anderson A, Tracey E, Friis S, McBride ML. Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab. 2006 May 1;91(5):1819-25.
9. McDonald AM, Lindeman B, Bahl D. Radioactive iodine: recognizing the need for risk-benefit balance. J Clin Oncol. 2022 May 1;40(13):1396-9.
10. Samhouri L, Kriz J, Elsayad K, Channaoui M, Pascher A, Riemann B, Wiewrodt R, Haverkamp U, Scobioala S, Eich HT. The Role of radiotherapy for patients with thyroid cancer in the modern era. Anticancer Res. 2020 Jun;40(6):3379-86.
11. Izkhakov E, Barchana M, Liphshitz I, Silverman BG, Stern N, Keinan-Boker L. Trends of second primary malignancy in patients with thyroid cancer: a population-based cohort study in israel. Thyroid. 2017 Jun;27(6):793-801.
12. Gandolfi G, Sancisi V, Piana S, Ciarrocchi A. Time to re-consider the meaning of BRAF V600E mutation in papillary thyroid carcinoma. Int J Cancer. 2015 Sep 1;137(5):1001-11.
13. Gilani SM, Abi-Raad R, Garritano J, Cai G, Prasad ML, Adeniran AJ. RAS mutation and associated risk of malignancy in the thyroid gland: An FNA study with cytology-histology correlation. Cancer Cytopathol. 2022 Apr;130(4):284-93.
14. Wirth LJ, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, Godbert Y, Barlesi F, Morris JC, Owonikoko TK, Tan DSW, Gautschi O, Weiss J, de la Fouchardière C, Burkard ME, Laskin J, Taylor MH, Kroiss M, Medioni J, Goldman JW, Bauer TM, Levy B, Zhu VW, Lakhani N, Moreno V, Ebata K, Nguyen M, Heirich D, Zhu EY, Huang X, Yang L, Kherani J, Rothenberg SM, Drilon A, Subbiah V, Shah MH, Cabanillas ME. Efficacy of Selpercatinib in RET-altered thyroid cancers. N Engl J Med. 2020 Aug 27;383(9):825-35.
15. Berthe E, Henry-Amar M, Michels JJ, Rame JP, Berthet P, Babin E, Icard P, Samama G, Galateau-Sallé F, Mahoudeau J, Bardet S. Risk of second primary cancer following differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 2004 May;31(5):685-91.
16. 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(3):384-9.
17. Rubino C, de Vathaire F, Dottorini ME, Hall P, Schvartz C, Couette JE, Dondon MG, Abbas MT, Langlois C, Schlumberger M. Second primary malignancies in thyroid cancer patients. Br J Cancer. 2003 Nov 3;89(9):1638-44.
18. Fallahi B, Adabi K, Majidi M, Fard-Esfahani A, Heshmat R, Larijani B, Haghpanah V. 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 Apr;36(4):277-82.
19. Cappagli V, Caldarella A, Manneschi G, Piaggi P, Bottici V, Agate L, Molinaro E, Bianchi F, Elisei R. Nonthyroidal second primary malignancies in differentiated thyroid cancer patients: Is the incidence increased comparing to the general population and could it be a radioiodine therapy consequence?. Int J Cancer. 2020 Nov 15;147(10):2838-46.
20. Tan H, Wang S, Huang F, Tong Z. Association between breast cancer and thyroid cancer risk: a two-sample Mendelian randomization study. Front Endocrinol (Lausanne). 2023 May 23;14:1138149.
21. Wang H, Li S, Shi J, Feng C, Wang Y, Zhang F. Unbalanced bidirectional causal association between thyroid cancer and ER-positive breast cancer: should we recommend screening for thyroid cancer in breast cancer patients? BMC Genomics. 2023 Dec 11;24(1):762.