Prevalence and treatment outcomes of second primary malignancies in Saudi patients with differentiated thyroid cancers

Khalid H. Al-Qahtani, MD, FRCCS, Mushabab Al-Asiri, MBBS, FRCS (Clin Oncol), Mutahir A. Tunio, MBBS, FCPS (Rad Oncol), Naji J. Aljohani, MD, FRCP, Yasser Bayoumi, MBChB, MD, Hussain Al-Hussain, MD, FRCP, Ahmed M. Maklad, MBChB, MD.

ABSTRACT

Objectives: To evaluate the clinicopathologic features, and explore the treatment outcomes of synchronous, or metachronous second primary malignancies (SPM) in conjunction with differentiated thyroid cancers (DTC).

Methods: This retrospective study was conducted on 823 DTC patients treated between 2000 and 2012 at 2 tertiary care hospitals (King Fahad Medical City and King Khalid University Hospital) in Riyadh, Kingdom of Saudi Arabia. Forty-one (5%) DTC patients were found to have SPM (61% metachronous and 39% synchronous). These patients with SPM were studied for clinicopathological features and treatment outcomes.

Results: The patients with DTC and SPM were older (median age: 54.3 years) than those without SPM (median age: 43.2 years); \( p=0.04 \). The frequency of SPM was breast (51.2%), colon (12.2%), kidney (7.3%), astrocytoma (7.3%), parotid (7.3%), rectum (4.9%), lymphoma (4.9%), nasopharynx (2.4%), and stomach (2.4%). Median follow-up was 8.05 years. Ten-year disease free survival, and overall survival (OS) rates were lower in DTC patients with SPM (56.1% for 10-year survival, and 71.7% for OS) than without SPM (95.5% for 10-year survival, and 97.8% for OS); \( p=0.0001 \). Metachronous SPM had better 10-year disease free survival rates (60.2%) than synchronous SPM (45%).

Conclusion: The co-occurrence of SPM with DTC affects long-term disease free survival and OS rates.

Saudi Med J 2015; Vol. 36 (4): 442-448
doi: 10.15537/smj.2015.4.10341

From the Department of Otolaryngology - Head and Neck Surgery (Al-Quhtani), College of Medicine, King Saud University, the Department of Radiation Oncology (Al-Asiri, Tunio, Al-Hussain), Comprehensive Cancer Center, the Department of Endocrinology and Thyroid Oncology (Aljohani), King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia, the Department of Radiation Oncology (Bayoumi), National Cancer Institute, Cairo University, Cairo, and the Department of Clinical Oncology (Maklad), Sohag University, Sohag, Egypt.

Received 22nd September 2014. Accepted 10th February 2015.

Address correspondence and reprint request to: Dr. Mutahir A. Tunio, Department of Radiation Oncology, Comprehensive Cancer Center King Fahad Medical City, PO Box 59046, Riyadh 11525, Kingdom of Saudi Arabia. Fax: +966 (11) 889999. E-mail: drmutahirtonio@hotmail.com
The incidence of differentiated thyroid cancers (DTC) including papillary and follicular cancers has increased exponentially over the past few years throughout the world with a wide geographic variation. In the Kingdom of Saudi Arabia, DTC has become the second most common malignancy behind only breast cancer, accounting for more than 10% of all cancers among women. One reason for increased identification of DTC is the use of high resolution neck ultrasonography (USG), and USG-guided fine needle aspiration biopsy (FNAB). The discovery of synchronous, or metachronous second primary malignancies (SPM) in these DTC patients is common. Several studies have reported a consensus increase in the risk of SPM among DTC primary patients, and this coexistence of SPM could be either random or associated with risk factors such as environmental, genetic predisposition, and radioactive iodine (131I) therapy related. A South Korean study by Cho et al reported 1.6% SPM in DTC patients, and that 131I therapy may play a role in future SPM risk. In a pooled analysis of 13 registries, a UK group discovered a 31% increase of SPM in DTC patients. Another study with Surveillance, Epidemiology, and End Results (SEER) data through 2002 reported a 9% increase in SPM in DTC patients. However, only a few studies examined the treatment outcomes including disease specific survival (DSS) and overall survival (OS) rates in DTC patients with SPM. There is a scarcity of information on treatment outcomes in DTC patients with SPM in the Kingdom of Saudi Arabia, where the DTC incidence rate is 5 per 100,000 people every year. Therefore, we aimed to evaluate the clinicopathologic features, explore the treatment outcomes of synchronous, or metachronous SPM in conjunction with DTC, and to compare these patients with a larger group of DTC patients without SPM; all patients were evaluated in the same period.

**Methods.** This retrospective study was carried out in 2 tertiary care hospitals (King Fahad Medical City and King Khalid University Hospital), Riyadh, Kingdom of Saudi Arabia. The study was conducted in accordance with the principles of the Helsinki Declaration, and with formal approval from the institutional ethical committee. The MEDLINE, CANCERLIT, Cochrane Library databases, and the Google search engine were searched to identify related research. Medical records of 823 patients with confirmed DTC, who were treated or followed up in 2 major tertiary care hospitals of Riyadh, Kingdom of Saudi Arabia, between July 2000 and December 2012 were reviewed using a computer based institutional database system. The DTC patients with SPM were retrieved in the following manner.

**Definitions.** The SPM were defined as “occurrence of another histopathologically confirmed malignancy at different anatomical site that must not be a recurrence or metastasis of the primary DTC”. Synchronous SPM was defined as SPM occurring within 6 months of the DTC diagnosis, and metachronous SPM was defined as SPM occurring more than 6 months after the DTC diagnosis.

**Exclusion criteria.** Patients with SPM occurring at least 6 months before the DTC diagnosis (pre-metachronous SPM) were excluded.

**Demographic, clinicopathological, and radiological variables.** Demographic, and clinical data including age at the diagnosis of DTC and SPM, gender, and symptomatology were reviewed. Different histopathological parameters, including the location of tumor, tumor size, histopathologic variants, multifocality, extrathyroidal extension, lymphovascular space invasion, surgical margin status, cervical lymph node status, background thyroid tissue, and types of SPM were also recorded. Data from different imaging modalities, including ultrasonography, whole body 131I scintigraphy, CT scan of neck, chest, abdomen, and pelvis, and fluorodeoxyglucose positron emission tomography was collected. Postoperative thyroid function tests, and thyroglobulin levels were also reviewed. Data regarding different treatment modalities, including the type of surgery, neck dissection types, adjuvant 131I, its dose regimens in millicurie, and the details of neck irradiation details (if given) were also recorded.

**Statistical analysis.** The primary endpoint was the disease free survival (DFS). Secondary points were; the frequency of SPM and types, and OS. Local recurrence of DTC was defined as, clinically or radiologically detectable recurrences in the thyroid bed or in cervical lymph nodes, and distant metastasis was defined as, clinically or radiologically detectable disease outside the neck. The DFS was defined as, the duration between the date of surgery, and the date of documented disease reappearance/relapse, death from cancer and/or last follow-up (censored). The OS was defined as, the duration between the date of surgery, and the date of patient death or last follow-up (censored). To compare DTC patients with and without SPM and...
shows the 10-year SPM-DFS rates in... and metachronous SPM as shown in Figures 1A and 1B. A total of 64 failures (all-site recurrences) (7.7%) were observed; 16/41 (15.9%) in DTC-SPM patients, and 48/782 (6.1%) in DTC patients without SPM (p=0.0001). The pattern of failures was: 3/64 patients (4.7%) had local neck recurrences (DTC-SPM; one patient, DTC without SPM; 2 patients) and 61/64 (95.3%) had distant metastasis (DTC-SPM; 14 patients, DTC without SPM; 47 patients). Combined locoregional and distant metastasis were seen in 2/41 (4.9%) DTC-SPM patients, and 1/782 (0.2%) in DTC without SPM patients (p=0.001). The lungs and bone were frequent sites of distant failure. All distant metastases were salvaged by 131I therapy and palliative irradiation for bony lesions (2 DTC without SPM patients). The 10-year DFS rates were 45% versus 60.2% in synchronous DTC-SPM, and metachronous DTC-SPM patients (p=0.034). The 10-year OS rates were 63.6% versus 76.5% in synchronous DTC-SPM and metachronous DTC-SPM patients (p=0.033) (Figures 2A & 2B). Figure 3A illustrates the 10-year DTC-DFS rates in synchronous, and metachronous DTC-SPM patients (poor in synchronous SPM), and Figure 3B shows the 10-year SPM-DFS rates in synchronous, and metachronous DTC-SPM with no difference (p=0.87).

Results. Among the 823 DTC patients in our departmental database, 41 (5%) patients were found to have SPM. The study cohort predominantly consisted of females (86%). The female to male ratio was 6.7. The median age of DTC diagnosis for the whole cohort was 44 years (range, 7.2-89.0). Most patients had papillary DTC (n = 707, 85.9%); only 116 (14.1%) patients had follicular DTC. The DTC patients with SPM were older (median age: 54.3 years) than their counterparts (median age: 43.2 years) (p=0.0001). There was no statistical significant difference between DTC patients with and without SPM regarding clinicopathological features and given treatment (Table 1).

For those patients with SPM, metachronous malignancies (61%) were more common as compared with synchronous (39%). The median time interval between DTC diagnosis and metachronous SPM diagnosis was 6.4 years (range, 2.0-7.8) and median time interval between DTC diagnosis and synchronous SPM was 2 months (0.1-3.5). Thirty-five of these patients (85.4%) received 131I therapy. The frequency of SPM in descending order was; breast (51.2%), colon (12.2%), kidney (7.3%), astrocytoma (7.3%), parotid (7.3%), rectum (4.9%), lymphoma (4.9%), nasopharynx (2.4%), and stomach (2.4%). Breast cancers were the most frequent metachronous SPM, and colon was most frequent synchronous SPM. Males had more colon cancers (4 patients; 9.8%). Synchronous SPM had more normal background thyroid tissue (56.2%) as compared with metachronous SPM (32%). One patient (15.9%) with synchronous SPM presented with distant metastasis in the lungs at the time of presentation. However, there was no statistical significant difference in clinicopathological features between synchronous and metachronous SPM as shown in Table 2.

Discussion. The key results of our analysis showed that the incidence of SPM is 5% after the diagnosis of DTC in Saudi Arabia; these DTC patients with SPM had poorer DFS and OS rates than those DTC without SPM, and the synchronous group had a poorer DFS and DTC-DFS; however, there was no difference in SPM-DFS between synchronous, and metachronous DTC-SPM. These results conflict with findings reported by similar Western studies.5,6,8,9 The low incidence of SPM in our series might be due to the relatively small sample size. Regarding the site of SPM, breast, and colon were dominant sites of SPM in our series, which concurs with those of other related studies, and one meta-analysis.5,6,8,9 Although, a causal relationship of 131I therapy and SPM was not the primary aim of our study, 85.4% of DTC-SPM received 131I therapy and could be a contributory factor for metachronous SPM as determined by other studies.13 However, 14.6% of DTC-SPM had no prior 131I therapy, which suggests that other factors may also be responsible for the increased incidence of SPM, including environmental risk factors initiating synchronous primaries, and genetic mutations.14,16

Interestingly, when comparing the synchronous with the metachronous DTC-SPM patients, we found that, despite a difference in the age of diagnosis for DTC, the age of SPM diagnosis was similar in both groups.
Table 1 - Characteristic differences between DTC patients with and without SPM.

| Variable                      | SPM - DTC | No SPM - DTC | P-value |
|-------------------------------|-----------|--------------|---------|
| Total patients                | 41/823 (5.0) | 782/823 (95.0) | < 0.0001* |
| *Age (years)                  | 54.3 (32-73) ± 8.8 | 43.2 (8-66) ± 12.3 |         |
| ≤45 years                     | 15 (36.6) | 500 (63.9) |         |
| >45 years                     | 26 (63.4) | 282 (36.1) |         |
| Gender                        |           |              |         |
| Female                        | 36 (87.8) | 672 (85.9) | 0.93* |
| Male                          | 5 (12.2) | 110 (14.1) |         |
| Histology                     |           |              |         |
| Papillary                     | 35 (85.4) | 669 (81.3) | 0.92* |
| Follicular                    | 6 (14.6) | 154 (18.7) |         |
| Type of surgery               |           |              |         |
| Near or total thyroidectomy   | 34 (82.9) | 652 (83.4) | 0.84* |
| Lobectomy                     | 7 (17.1) | 130 (16.6) |         |
| Lymph node surgery            |           |              |         |
| Central neck dissection       | 25 (60.9) | 461 (58.9) |         |
| Lateral neck dissection       | 11 (26.8) | 156 (19.9) |         |
| Sampling                      | 3 (7.3) | 150 (19.2) |         |
| None                          | 2 (5.0) | 15 (2.0) |         |
| Mean size (cm)                |           |              |         |
| ≤2 cm                         | 27 (65.8) | 508 (64.9) | 0.84* |
| >2 cm                         | 40 (34.2) | 274 (35.1) |         |
| Location (dominant mass)      |           |              |         |
| Right lobe                    | 6 (14.6) | 171 (21.9) |         |
| Left lobe                     | 11 (26.8) | 189 (24.2) | 0.90* |
| Isthmus                       | 5 (12.2) | 101 (12.9) |         |
| Bilateral                     | 19 (46.4) | 321 (41.0) |         |
| Multifocal                    |           |              |         |
| Yes                           | 21 (51.2) | 352 (45.0) | 0.90* |
| No                            | 20 (48.8) | 430 (55.0) |         |
| ETE                           |           |              |         |
| Yes                           | 14 (34.2) | 281 (35.9) | 0.83* |
| No                            | 27 (65.8) | 501 (64.1) |         |
| LVSI                          |           |              |         |
| Yes                           | 12 (29.3) | 229 (29.3) | 1.2* |
| No                            | 29 (70.7) | 553 (70.7) |         |
| Surgical margins              |           |              |         |
| Positive                      | 14 (34.2) | 276 (35.3) | 0.83* |
| Negative                      | 27 (65.8) | 506 (64.7) |         |
| Lymph node metastasis         |           |              |         |
| Yes                           | 18 (43.9) | 355 (45.4) |         |
| N1a                           | 12 (66.7) | 232 (65.4) | 0.76* |
| N1b                           | 6 (33.3) | 123 (34.6) |         |
| N0                            | 23 (56.1) | 427 (54.6) |         |
| Background thyroid tissue     |           |              |         |
| Normal                        | 17 (41.5) | 328 (41.9) |         |
| Multi-nodular goiter          | 6 (14.6) | 122 (15.6) | 0.75* |
| lymphocytic thyroiditis       | 12 (29.3) | 217 (27.8) |         |
| Hashimotos’ thyroiditis       | 6 (14.6) | 115 (14.7) |         |
| Distant metastasis at presentation | 1 (2.4) | 24 (3.1) | 0.90* |
| pT staging                    |           |              |         |
| T1                             | 11 (26.8) | 226 (28.9) |         |
| T2                             | 19 (46.4) | 346 (44.3) | 1.1* |
| T3                             | 9 (21.9) | 191 (24.4) |         |
| T4                             | 2 (4.9) | 19 (2.4) |         |
| Mean postoperative TG (ng/ml) | 2.44 (0.1-42890) | 2.39 (0.1-34550) | 0.62* |
| I-131 dose                    |           |              |         |
| No                            | 6 (14.6) | 85 (10.8) |         |
| 30 mCi                         | 5 (12.2) | 54 (6.9) |         |
| >100 mCi                      | 15 (36.6) | 299 (38.3) | 0.76* |
| >150 mCi                      | 15 (36.6) | 344 (44.0) |         |
| More than one ablation         | 11 (26.8) | 191 (24.4) |         |
| RT to neck                    | 1 (2.4) | 19 (2.4) | 0.82* |

*Calculated at the time of second primary malignancy diagnosis.

* Students’ Independent t test, SPM - second primary malignancy, DTC - differentiated thyroid cancers, I-131 - radioactive iodine 131, SD - standard deviation, ETE - extrathyroidal extension, LVSI - lymphovascular space invasion, pT - primary tumor, TG - thyroglobulin, mCi - millicurie, RT - radiation therapy .

(above 50 years), which is consistent with the findings of Lang et al.9 These results confirm that SPM tended to be found at a certain age group (above 50 years), and this age group of patients are potential candidates for surveillance (especially for breast, and colon). It is also worth mentioning that there was no significant difference
Second primary malignancies in thyroid cancer ... Al-Qahtani et al

Table 2 - Patients’ characteristics of differentiated thyroid cancers with synchronous and metachronous second primary malignancy (SPM).

| Variable | Synchronous SPM | Metachronous SPM | P-value |
|----------|-----------------|------------------|---------|
| Total number of patients | 16/41 (39.0) | 25/41 (61.0) | 0.001a |
| Age (years) at DTC diagnosis | 57.4 (46-67) | 43.7 (30-56) | 0.051a |
| Age (years) at SPM diagnosis | 57.4 (46-67) | 50.1 (32-62) | 0.72 |
| Gender | | | | 0.72b |
| Female | 12 (75.0) | 19 (76.0) | |
| Male | 4 (25.0) | 6 (24.0) | |
| Type of surgery | | | | |
| Near or total thyroidectomy | 15 (93.7) | 23 (92.0) | 0.71b |
| Lobectomy | 1 (6.3) | 2 (8.0) | |
| Type of SPM | | | | 0.001b |
| Breast | 2 (12.5) | 19 (76.0) | |
| Colon | 3 (18.7) | 2 (8.0) | |
| Rectum | 2 (12.5) | 0 (0) | |
| Astrocytoma | 1 (6.3) | 2 (8.0) | |
| Gastric | 1 (6.3) | 0 (0) | |
| Parotid | 2 (12.5) | 1 (4.0) | |
| Nasopharynx | 1 (6.3) | 0 (0) | |
| Kidney | 2 (12.5) | 1 (4.0) | |
| Hodgkin’s lymphoma | 2 (12.5) | 0 (0) | |
| TNM staging | | | | |
| pT2N0M0 | 1 (6.3) | 8 (32.0) | |
| pT3N0M0 | 1 (6.3) | 4 (16.0) | |
| pT2/T3N1M0 | 0 (0) | 7 (28.0) | 0.001a |
| Colon/rectum | | | 0.001b |
| pT2N1M0 | 4 (25.0) | 1 (4.0) | |
| pT1N1M0 | 1 (6.3) | 1 (4.0) | 0.01b |
| Astrocytoma | | | | 0.91a |
| Low grade | 0 (0) | 0 (0) | |
| High grade | 1 (6.3) | 2 (8.0) | |
| Gastric | | | | 0.4a |
| pT3N1M0 | 1 (6.3) | 0 (0) | |
| Parotid | | | | 0.04a |
| pT3N0M0 | 2 (12.5) | 1 (4.0) | |
| Nasopharynx | 1 (6.3) | 0 (0) | |
| cT3N2M0 | | | |
| Kidney | | | | 0.04a |
| pT2N0M0 | 1 (6.3) | 1 (4.0) | 0.04a |
| pT3N0M0 | | | |
| Mean size (cm) | 3.0 (0.8-9.5) | 2.7 (0.1-7) | 0.096b |
| Location (dominant mass) | | | | |
| Right lobe | 2 (12.5) | 4 (16.0) | |
| Left lobe | 6 (37.5) | 5 (20.0) | |
| Isthmus | 3 (18.7) | 2 (8.0) | 0.052b |
| Bilateral | 5 (31.3) | 14 (56.0) | |
| Multifocal (positive) | 9 (56.3) | 12 (48.0) | 0.051a |
| ETE (positive) | 6 (37.5) | 8 (32.0) | 0.064b |
| LVSI (positive) | 5 (31.3) | 7 (28.0) | 0.71b |
| Lymph node metastasis | 8 (50.0) | 10 (40.0) | 0.54a |
| Background thyroid tissue | | | | |
| Normal | 9 (56.2) | 8 (32.0) | |
| Multi-nodular goiter | 2 (18.7) | 4 (16.0) | |
| Lymphocytic thyroiditis | 4 (27.3) | 8 (32.0) | |
| Hashimoto’s thyroiditis | 1 (15.9) | 5 (16.0) | |
| Distant Metastasis at presentation | 1 (15.9) | 0 (0) | 0.001 |
| pT staging | | | | |
| T1 | 4 (25.0) | 7 (16.0) | |
| T2 | 8 (50.0) | 11 (44.0) | 0.72 |
| T3 | 3 (18.7) | 6 (24.0) | |
| T4 | 1 (15.9) | 1 (4.0) | |
| 131I dose (given) | 14 (87.5) | 21 (84.0) | 0.70 |
| RT to neck | 1 (15.9) | 0 (0) | 0.001 |

*a* Student’s independent t test, *b* Fisher exact test, DTC - differentiated thyroid cancers, 

131I - radioactive iodine 131, SD - standard deviation, ETE - extrathyroidal extension, LVSI - lymphovascular space invasion, pT - primary tumor, RT - radiation therapy.
Second primary malignancies in thyroid cancer ... Al-Qahtani et al

Figure 1 - Kaplan-Meier curves of: A) disease specific survival, and B) overall survival in patients with differentiated thyroid cancers with or without second primary malignancy.

Figure 2 - Kaplan-Meier curves of: A) disease specific survival, and B) overall survival in patients with differentiated thyroid cancers with synchronous and metachronous second primary malignancy.

Figure 3 - Kaplan-Meier curves of: A) differentiated thyroid cancer related disease specific survival (DSS), and B) second primary malignancy related disease specific survival DSS in patients with differentiated thyroid cancers (DTC) with synchronous and metachronous second primary malignancy.
between DTC in synchronous and metachronous DTC-SPM patients regarding primary tumor size and other clinicopathological characteristics; only one patient (15.9%) with synchronous SPM presented with distant metastasis at the time of presentation. Although, all patients with synchronous DTC-SPM were staged also on PET-PCT imaging as routine, the results are different from the study of Lang et al.,

but consistent with the study of Omur et al. Breast cancer was the predominant SPM in our series, which was found in agreement with the SEER program statistics, in which breast cancer amounted to 36% of all SPM in women with thyroid cancer, depending on age, and especially for women under 40 years with a standardized incidence ratio 1.4. However, Verkooijen et al.,

found that in patients with thyroid cancers the incidence of breast cancer as a SPM is higher than the general population, which was attributed to common etiological (hormonal) or genetic causes. Similarly, in the California Cancer Registry; 10,932 women with DTC, the risk of in situ breast cancer, but not for invasive breast cancer, was significantly increased. We also found that the certain SPM types (astrocytomas, and parotid glands), which were observed in the present study have not been addressed in other studies. The presence of these SPM could explain the slightly lower DFS rates in our cohort. A limitation of this study was its retrospective nature with low sample size.

In conclusion, SPM accounts for 5% in Saudi patients with DTC. These DTC patients with SPM have a poorer prognosis in terms of DFS and OS rates compared with those without SPM. Patients with synchronous DTC-SPM were more likely to die from SPM mainly because of aggressive and advanced cancer types compared with those with metachronous DTC-SPM. Breast, and colonic cancers were predominant SPM, which warrants active surveillance for these groups. Also, emphasis should be placed on patient education for regular follow ups with their treating physicians.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin 2009; 59: 225-249.
2. Hussain F, Iqbal S, Mehmood A, Bazarbashi S, El-Hassan T, Chaudhri N. Incidence of thyroid cancer in the Kingdom of Saudi Arabia, 2000-2010. Hematol Oncol Stem Cell Ther 2013; 6: 58-64.
3. Ruggieri M, Fumarola A, Straniero A, Maiuolo A, Coletta I, Veltri A, et al. The estimation of the thyroid volume before surgery--an important prerequisite for minimally invasive thyroidectomy. Langenbecks Arch Surg 2008; 393: 721-724.
4. Hsu CH, Huang CL, Hsu YH, Iqbal U, Nguyen PA, Jian WS. Co-occurrence of second primary malignancy in patients with thyroid cancer. QJM 2014; 107: 643-648.
5. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD, et al. Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid 2009; 19: 451-457.
6. Cho YY, Lim J, Oh CM, Ryu J, Jung KW, Chung JH, et al. Elevated risks of subsequent primary malignancies in patients with thyroid cancer: A nationwide, population-based study in Korea. Cancer 2015; 121: 259-268.
7. Sandeep TC, Strachan MW, Reynolds RM, Brewster DH, Scelo G, Pukkala E, et al. Second primary cancers in thyroid cancer patients: a multinational record linkage study. J Clin Endocrinol Metab 2006; 91: 1819-1825.
8. Brown AP, Chen J, Hitchcock YJ, Szabo A, Shrieve DC, Tward JD. The risk of second primary malignancies up to three decades after the treatment of differentiated thyroid cancer. J Clin Endocrinol Metab 2008; 93: 504-515.
9. Lang BH, Lo CY, Wong IO, Cowling BJ. Impact of second primary malignancy on outcomes of differentiated thyroid carcinoma. Surgery 2010; 148: 1191-1196.
10. Omur O, Ozcan Z, Yazici B, Akgun A, Oral A, Ozkilic H. Multiple primary tumors in differentiated thyroid carcinoma and relationship to thyroid cancer outcome. Endocer J 2008; 55: 365-372.
11. Alghamdi IG, Hussain II, Alghamdi MS, Dohal AA, Almalki SS, El-Sheemy MA. The Incidence Rate of Thyroid Cancer Among Women in Saudi Arabia: An Observational Descriptive Epidemiological Analysis of Data from Saudi Cancer Registry 2001-2008. J Immmun Minor Health 2014 May 25. [Epub]
12. Yang YH. [A path analysis on factors influencing second primary cancer screening practices in stomach, colon, and breast cancer survivors]. J Korean Acad Nurs 2014; 44: 139-148. Korean.
13. Lang BH, Wong IO, Wong KP, Cowling BJ, Wan KY. Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery 2012; 151: 844-850.
14. Ngeow J, Stanuch K, Mester JL, Barnholtz-Sloan JS, Eng C. Second malignant neoplasms in patients with Cowden syndrome with underlying germline PTEN mutations. J Clin Oncol 2014; 32: 1818-1824.
15. Van Fossen VL, Wilhelm SM, Eaton JL, McHenry CR. Association of thyroid, breast and renal cell cancer: a population-based study of the prevalence of second malignancies. Ann Surg Oncol 2013; 20: 1341-1347.
16. Consorti F, Di Tanna G, Milazzo F, Antonaci A. Nulliparity enhances the risk of second primary malignancy of the breast in a cohort of women treated for thyroid cancer. World J Surg Oncol 2011; 9: 88.
17. Curtis RE, Freedman DM, Ron E, Ries LAG, Hacker DG, Edwards BK, et al, editors. New Malignancies Among Cancer Survivors: SEER Cancer Registries, 1973-2000. Bethesda (MD): National Cancer Institute, National Institutes of Health; 2006.
18. Verkooijen RB, Smit JW, Romijn JA, Stokkel MP. The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer. Eur J Endocrinol 2006; 155: 801-806.
19. Bhattacharyya N, Chien W. Risk of second primary malignancy after radioactive iodine treatment for differentiated thyroid carcinoma. Ann Otol Rhinol Laryngol 2006; 115: 607-610.