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

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ABSTRACT

الأهداف: تقييم الصفات الباثولوجية السريرية، وتحليل نتائج العلاج بين المرضى المصابين بالأمراض الخبيثة الأولية الثانية المزامنة أو الغير متزامنة، بالإضافة إلى الإصابة بسرطان الغدة التفريقي.

الطريقة: شملت هذه الدراسة الاستطلاعية 823 حالة سرطان للغدة الدرقية والذين تلقوا علاجهم خلال الفترة من 2000م إلى 2012م وذلك في مستشفيين متخصصين وهما مدينة الملك فهد الطبية ومستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية . ولقد عانى 41 من الحالات (5%) المصابة بسرطان الغدة الدرقية من ورم أولي ثانوي (39% منها متزامن مع أورام أخرى، و61% غير متزامن).

النتائج: أشارت نتائج الدراسة بأن مرضى سرطان الغدة الدرقية كأورام ثانوية قد كانوا أكبر سناً (متوسط العمر: 54.3 عاماً) وذلك بالمقارنة مع من لم يظهر لهم سرطان الغدة الدرقية كأورام ثانوية (متوسط العمر 43.2 عاماً) (p=0.04). ولقد كان توزيع الحالات حسب تشخيص السرطان الأولي كالآتي: الثدي (51.2%)، القولون (12.2%)، الكلى (7.3%)، الورم النجمي الدماغي (7.3%)، ورم الغدة النكفية (7.3%)، المستقيم (4.9%)، الغدد الليمفاوية (4.9%)، البلعوم الأنفي (2.4%) وأخيراً المعدة (2.4%). وقد كان متوسط فترة المتابعة 8.05عاماً. فيما كان معدل احتمال البقاء بدون المرض لمدة 10 سنوات، والمعدل العام لاحتمال البقاء على قيد الحياة أقل بالنسبة للحالات التي تم تشخيصها بسرطان الغدة الدرقية كأورام ثانوية (56.1% بالنسبة لاحتمال البقاء 10 سنوات، 71.7% بالنسبة للمعدل العام لاحتمال البقاء على قيد الحياة) وذلك بالمقارنة مع المرضى الذين لم يشخص لديهم سرطان الغدة الدرقية كورم ثانوي (95.5% بالنسبة لاحتمال البقاء 10 سنوات، 97.8% بالنسبة للمعدل العام لاحتمال البقاء على قيد الحياة) (p=0.0001). وكانت الحالات التي تم تشخيصها بسرطان الغدة الدرقية كأورام ثانوية غير متزامنة مع أورام أخرى أفضل من حيث احتمالية البقاء على قيد الحياة (60.2%) مقارنةً بالحالات التي تم تشخيصها بالتزامن مع أورام ثانوية (45%).

الخاتمة: أظهرت الدراسة تأثير سرطان الغدة الدرقية كأورام ثانوية على المدى البعيد على احتمالية البقاء على قيد الحياة على المدى البعيد، وأيضا المعدل العام لاحتمال البقاء على قيد الحياة.

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.

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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.[1] 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.[2] One reason for increased identification of DTC is the use of high resolution neck ultrasonography (USG), and USG-guided fine needle aspiration biopsy (FNAB).[3] The discovery of synchronous, or metachronous second primary malignancies (SPM) in these DTC patients is common.[4] Several studies have reported a consensus increase in the risk of SPM among DTC primary patients, and this co-existence of SPM could be either random or associated with risk factors such as environmental, genetic predisposition, and radioactive iodine (^{131}I) therapy related.[5] A South Korean study by Cho et al[6] reported 1.6% SPM in DTC patients, and that ^{131}I 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.[7] Another study with Surveillance, Epidemiology, and End Results (SEER) data through 2002 reported a 9% increase in SPM in DTC patients.[8] However, only a few studies examined the treatment outcomes including disease specific survival (DSS) and overall survival (OS) rates in DTC patients with SPM.[9,10] 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.[11] 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.[12]

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 ^{131}I 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 ^{131}I, 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

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synchronous, and metachronous SPM groups, Student's t test, or Fisher exact tests were used to determine the differences in various clinical variables. Probabilities of DFS, and OS were shown with the Kaplan-Meier method, and the comparisons for various survival curves were performed using log rank. A *p*-value <0.05 was considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 16.0.

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 ^{131}I 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**.

Disease free and overall survival rates. A median follow-up period was 8.05 years (range: 1.62-11.4). The 10-year DFS rate for DTC patients without SPM was 95.5%, and the OS rate was 97.8%. The 10 year DFS rate for DTC patients with SPM was 56.1%, and OS rate was 71.7% (*p*=0.0001) **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 distance 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*=0001). The lungs and bone were frequent sites of distant failure. All distant metastases were salvaged by ^{131}I 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).

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.[6-10] 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 ^{131}I therapy and SPM was not the primary aim of our study, 85.4% of DTC-SPM received ^{131}I 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 ^{131}I 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 n (%)	No SPM-DTC n (%)	*P*-value
Total patients	41/823 (5.0)	782/823 (95.0)	< 0.0001[a]
[*]Age (years)	54.3 (32-73) ± 8.8	43.2 (8-66) ± 12.3	
≤45 years	15 (36.6)	500 (63.9)	0.0001[a]
≥45 years	26 (63.4)	282 (36.1)	
Gender			
Female	36 (87.8)	672 (85.9)	0.93[a]
Male	5 (12.2)	110 (14.1)	
Histology			
Papillary	35 (85.4)	669 (81.3)	0.92[a]
Follicular	6 (14.6)	154 (18.7)	
Type of surgery			
Near or total thyroidectomy	34 (82.9)	652 (83.4)	0.84[a]
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)	0.77[a]
Sampling	3 (7.3)	150 (19.2)	
None	2 (5.0)	15 (2.0)	
Mean size (cm)	2.76 (0.1-9.8) ± 2.1	2.74 (0.1-9.9) ± 1.9	
≤2 cm	27 (65.8)	508 (64.9)	0.84[a]
≥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[a]
Isthmus	5 (12.2)	101 (12.9)	
Bilateral	19 (46.4)	321 (41.0)	
Multifocal			
Yes	21 (51.2)	352 (45.0)	0.90[a]
No	20 (48.8)	430 (55.0)	
ETE			
Yes	14 (34.2)	281 (35.9)	0.83[a]
No	27 (65.8)	501 (64.1)	
LVSI			
Yes	12 (29.3)	229 (29.3)	1.2[a]
No	29 (70.7)	553 (70.7)	
Surgical margins			
Positive	14 (34.2)	276 (35.3)	0.83[a]
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[a]
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[a]
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[a]
pT staging			
T1	11 (26.8)	226 (28.9)	
T2	19 (46.4)	346 (44.3)	1.1[a]
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[a]
I-131 dose			
No	6 (14.6)	85 (10.8)	
30 mCi	5 (12.2)	54 (6.9)	0.76[a]
100 mCi	15 (36.6)	299 (38.3)	
> 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[a]

[*]Calculated at the time of second primary malignancy diagnosis,
[a] Student's 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

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

Variable	Synchronous SPM	Metachronous SPM	*P*-value
	n (%)		
Total number of patients	16/41 (39.0)	25/41 (61.0)	0.001[a]
Age (years) at DTC diagnosis	57.4 (46-67)	43.7 (30-56)	0.051[a]
Age (years) at SPM diagnosis	57.4 (46-67)	50.1 (32-62)	0.72
Gender			
Female	12 (75.0)	19 (76.0)	0.72[b]
Male	4 (25.0)	6 (24.0)	
Type of surgery			
Near or total thyroidectomy	15 (93.7)	23 (92.0)	0.71[b]
Lobectomy	1 (6.3)	2 (8.0)	
Type of SPM			
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)	0.001[b]
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			
Breast			
pT2N0M0	1 (6.3)	8 (32.0)	
pT3N0M0	1 (6.3)	4 (16.0)	
pT2/T3N1M0	0 (0)	7 (28.0)	0.001[a]
Colon/rectum			
pT3N0M0	4 (25.0)	1 (4.0)	
pT2N1M0	1 (6.3)	1 (4.0)	0.01[b]
Astrocytoma			
Low grade	0 (0)	0 (0)	
High grade	1 (6.3)	2 (8.0)	0.91[a]
Gastric			
pT3N1M0	1 (6.3)	0 (0)	0.04[a]
Parotid			
pT3N0M0	2 (12.5)	1 (4.0)	
Nasopharynx			
cT3N2M0	1 (6.3)	0 (0)	0.04[a]
Kidney			
pT2N0M0	1 (6.3)	0 (0)	
pT3N0M0	1 (6.3)	1 (4.0)	0.04[a]
Mean size (cm)	3.0 (0.8-9.5)	2.7 (0.1-7)	0.096[b]
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)	0.052[b]
Bilateral	5 (31.3)	14 (56.0)	
Multifocal (positive)	9 (56.3)	12 (48.0)	0.051[a]
ETE (positive)	6 (37.5)	8 (32.0)	0.064[b]
LVSI (positive)	5 (31.3)	7 (28.0)	0.71[b]
Lymph node metastasis	8 (50.0)	10 (40.0)	0.54[a]
Background thyroid tissue			
Normal	9 (56.2)	8 (32.0)	
Multi-nodular goiter	2 (18.7)	4 (16.0)	0.04[b]
Lymphocytic thyroiditis	4 (27.3)	8 (28.0)	
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)	
^{131}I 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, ^{131}I - radioactive iodine 131, SD - standard deviation, ETE - extrathyroidal extension, LVSI - lymphovascular space invasion, pT - primary tumor, RT - radiation therapy

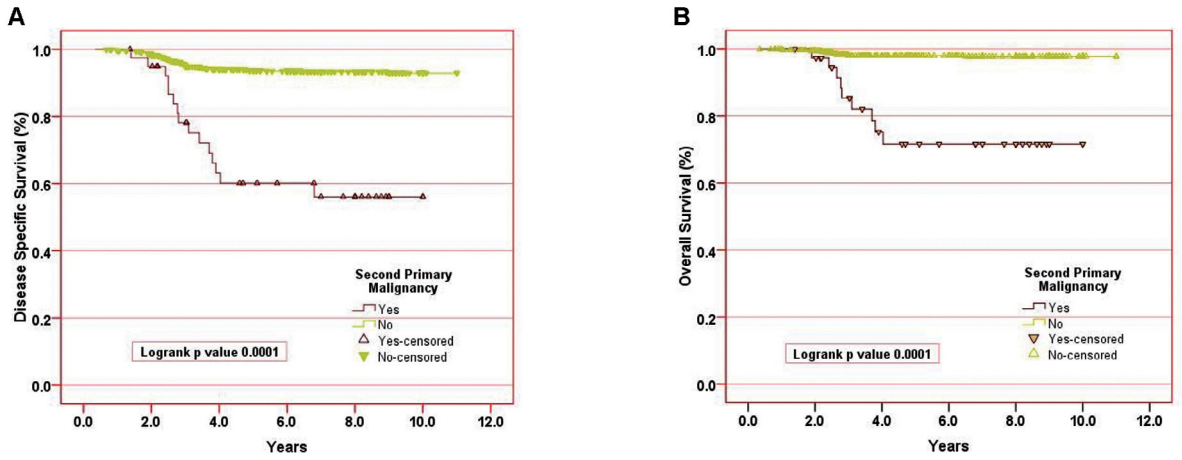

Figure 1 - Kaplan-Meier curves of: **A**) disease specific survival, and **B**) overall survival in patients with differentiated thyroid cancers with or without second primary malignancy.

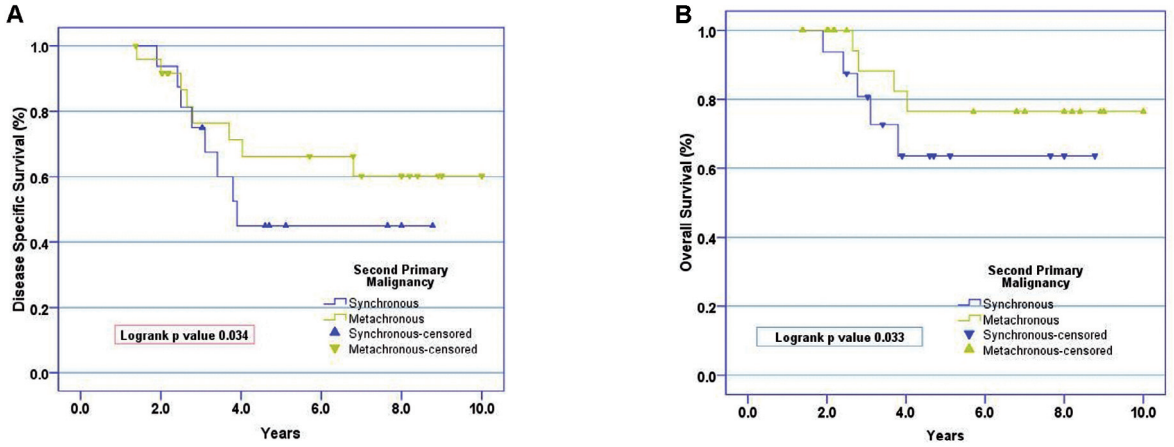

Figure 2 - Kaplan-Meier curves of: **A**) disease specific survival, and **B**) overall survival in patients with differentiated thyroid cancers with synchronous and metachronous second primary malignancy.

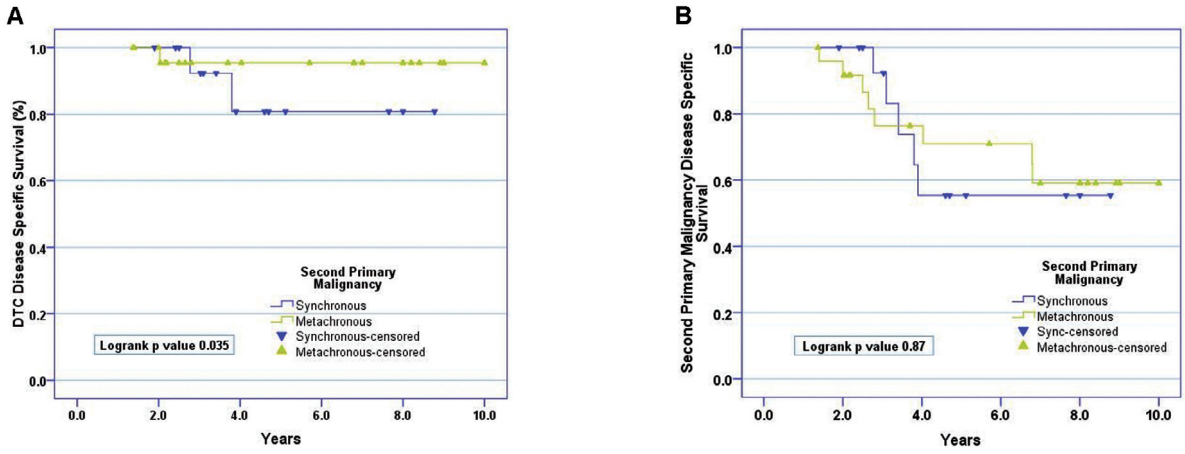

Figure 3 - Kaplan-Meier curves of: **A**) differentiated thyroid cancer related disease specific survival (DSS), and **B**) second primary malignancy related disease specific survival DSS in patients with differentiated thyroid cancers (DTC) with synchronous and metachronous second primary malignancy.

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,[9] but consistent with the study of Omur et al.[10] Breast cancer was the predominant SPM in our series, which was found in agreement with the SEER program statistics,[17] 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.[17] However, Verkooijen et al,[18] 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.[19] 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.[8-10] 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.

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