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RESEARCH ARTICLE

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Incidence of Second Primary Malignancies Following Thyroid Cancer Treatment with Radioactive Iodine

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ABSTRACT

Background: Thyroid cancer is the most common endocrine malignancy, with an increasing incidence globally and in Oman. The standard treatment for differentiated thyroid cancer (DTC) involves radioactive iodine (RAI). However, previous studies have suggested that RAI treatment may increase the risk of second primary malignancies (SPM). Despite the high incidence of thyroid cancer in Oman, to our knowledge, there are no published reports on the association between RAI treatment and the risk of SPM in Oman.

Objective: There is a lot of debate about the possibility of developing SPM in DTC patients after treatment with RAI. This research aimed to evaluate the incidence and estimate the risk of SPM in thyroid cancer patients treated with RAI.

Materials and Methods: A retrospective cohort study was conducted at Sultan Qaboos University Hospital (SQUH) for 500 DTC patients who received RAI treatment between January 2007 and December 2017. We collected patients' information, including gender, age at diagnosis, thyroid cancer subtypes, site of SPM, cumulative RAI doses, and follow-up period. Descriptive statistics and Mann-Whitney test were used to analyze the data. SPM was defined as a new malignancy diagnosed at least one year after the first RAI dose.

Results: The mean follow-up period was 9.5 ± 3 years (range 5.1-15.8). During this period, four patients (0.8%) developed SPMs, all with the papillary subtype. The sites of the SPMs were the colon, bladder, breast, and liver. The Mann-Whitney test, comparing cumulative RAI doses between the high-dose and SPM groups, yielded a significant p-value (<0.001).

Conclusion: The incidence of SPMs in patients with thyroid cancer treated with RAI is low, and age at diagnosis was found to be the only significant predictor of SPM occurrence. Further studies with larger sample sizes and extended follow-up periods are recommended to confirm these findings.

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Radioactive Iodine, Second Primary Malignancy, Thyroid Cancer

Introduction

Background

Thyroid cancer is the most common endocrine malignancy, representing over 90% of all cases of endocrine cancers [1]. The incidence of thyroid cancer has been steadily increasing globally over the past few decades, particularly in the case of papillary thyroid cancer (PTC), the most common subtype of thyroid cancer [2]. In Oman, thyroid cancer is the second most common cancer among women, with an incidence rate of 7.6 cases per 100,000 population. The incidence has been increasing in recent years in line with the global trend [3].

The standard treatment for differentiated thyroid cancer (DTC), which includes PTC and follicular thyroid cancer, is total or near-total thyroidectomy followed by RAI treatment [4]. RAI therapy involves administering a radioactive iodine isotope, usually iodine-131, to destroy any remaining thyroid tissue and cancer cells that may have spread to nearby lymph nodes or distant organs [4]. RAI treatment has been shown to improve disease-specific survival and reduce the risk of recurrence in DTC patients [4].

However, previous studies have suggested that RAI treatment may increase the risk of SPMs, defined as new primary malignancies in patients previously diagnosed with cancer [5]. The mechanisms underlying the association between RAI treatment and SPMs are poorly understood but may include the carcinogenic effects of radiation exposure, genetic predisposition, and environmental factors [6]. Several studies have reported an increased incidence of SPMs in thyroid cancer patients who have received RAI treatment [5,7]. On the other hand, other studies have found no association between RAI and the risk of SPMs [8,6]. These conflicting findings may be due to differences in study design, patient population, or length of follow-up. Despite the high incidence of thyroid cancer in Oman, little is known about the association between

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RAI treatment and the risk of SPMs in this population. However, the exact risk and pattern of SPMs in thyroid cancer survivors remain unclear, and the potential risk factors for SPMs after RAI treatment are not well defined.

Rational

The use of RAI in treating DTC has been shown to improve disease-specific survival and reduce the risk of recurrence in DTC patients. However, there is a concern that RAI treatment may increase the risk of SPMs. The exact risk and sites of SPMs in thyroid cancer survivors after RAI treatment are not well defined, and the mechanisms underlying the association are poorly understood. Previous studies have reported conflicting results on the association, and no previous research has been conducted in Oman to investigate this relationship. This study will provide critical information on the long-term health outcomes of thyroid cancer survivors in Oman and inform the development of clinical management and surveillance strategies for this population.

Aim of the Study

This retrospective cohort study aims to investigate the incidence, risk factors, and sites of second primary malignancies after radioactive iodine treatment among thyroid cancer patients in Oman.

Specific Objectives

1. To determine the incidence of SPM in thyroid cancer patients treated with RAI at SQUH.
2. To identify the sites of SPMs that occur in thyroid cancer patients after RAI treatment.
3. To evaluate other possible factors associated with SPMs in DTC survivors, including age at diagnosis of thyroid cancer, gender, histological subtype, cumulative RAI activity, and follow-up period.
4. To compare the incidence and sites of SPMs in thyroid cancer patients treated with RAI at SQUH to those reported in other populations and the literature.

Material and Methods

Study Setting

The study was conducted in the Radiology department at SQUH, a tertiary healthcare hospital in the Governate of Muscat, Sultanate of Oman.

Study Design and Population

This study is a retrospective study of thyroid cancer patients treated with RAI in SQUH.

From 720 patients with histopathological diagnoses of thyroid cancer treated with RAI at the SQUH over 11 years between January 1, 2007, and December 31, 2017, 500 met the inclusion and exclusion criteria.

Inclusion Criteria

1. Patients received RAI treatment for thyroid cancer between 2007 and 2017.
2. Patients completed their treatment courses at SQUH.

Exclusion Criteria

1. Patients were transferred to SQUH to take RAI only (missing follow-up).
2. Prior SPM (before RAI treatment) or synchronous SPM (in the first year of treatment).

Data Collection

Data were collected from the Hospital Information System (TrackCare®), which is the electronic medical record (EMR) system used at SQUH. We recorded in the datasheet information of each case, including gender, age at diagnosis, thyroid cancer subtypes, the first dose and the subsequent cumulative RAI doses, follow-up period, and data about the SPM (age at diagnosis, site). All patients were given a routine and periodic follow-up schedule for thyroid cancer that included cervical ultrasounds every 6–12 months and measurements of serum thyroglobulin. Where clinically necessary, additional complementary tests like computed tomography (CT) and a whole-body scan (WBS) were carried out in a tailored manner. There was no ongoing screening for other cancers. Only formally diagnosed non-thyroid neoplasms were taken into consideration. After a complementary study and the presence of indicative symptoms and indicators, SPM was determined to be the cause. The data were collected retrospectively from 6/2022 to 12/2022.

Statistical Analysis

Statistical analysis was performed using SPSS version 23 (Statistical Package for the Social Sciences). Descriptive statistics were used to summarize the patient's demographic and clinical characteristics, including mean, standard deviation, median, range, frequency, and percentage. The incidence of SPM was calculated. The results were presented in tables.

Ethical Approval

The Medical Research Ethics Committee (MREC) at SQUH approved the study on 30th May 2022 (MREC #2777). All patient's data were kept confidential and anonymized to protect patient privacy.

Results

A total of 500 patients with thyroid cancer who underwent RAI treatment were included in this study. The mean age at diagnosis was 37.2 ± 12.7 years (range 4-84), and most of the patients were female (409, 81.8%). The mean follow-up period was 9.5 ± 3 years (range 5.1-15.8). The most common thyroid cancer subtypes were papillary (441, 88.2%) and follicular (53, 10.6%), with the remaining six patients (1.2%) having other subtypes.

Table 1: Baseline Characteristics of the Entire Population Studied (n = 500)

Characteristic		Value
Total number of patients		500
Age at diagnosis of DTC (years)		37.2 (± 12.7 years)
Gender (n, %)	Female	409 (81.8%)
	Male	91 (18.2%)
Follow-up period (years)		9.5 (± 3)
Thyroid cancer subtypes (n, %)	Papillary	441 (88.2%)
	Follicular	53 (10.6%)
	Others*	6 (1.2%)
Cumulative RAI (GBq)		3.45 (42.7)

Values are represented by mean (±SD), number of patients (%), or median (range). GBq: The SI unit of measurement of radioactivity.

*Others include Medullary (0.8%) and Anaplastic (0.4%).

During the follow-up period, four patients (0.8%) developed a second primary malignancy, all of them with the papillary subtype. Two of the patients were male, and two were female. The sites of the second primary malignancy were the colon, bladder, breast, and liver. Table 2 describes the individual characteristics of the four patients.

Table 2: Individual Characteristics of Patients who Developed SPM

No.	Gender	DTC histological subtype	Age at RAI exposure (years)	Age at SPM diagnosis (years)	Cumulative RAI activity (GBq)	Latency period (years)	SPM subtype
1	F	PTC	47	54.6	3.52	7.6	Colon
2	M	PTC	63	66	3.4	3	Bladder
3	F	PTC	40	53.4	3.3	3.4	Breast
4	M	PTC	57	64.8	2.57	7.8	Liver

DTC: differentiated thyroid cancer; SPM: second primary malignancy; RAI: radioactive iodine treatment; PTC: papillary thyroid cancer; GBq: The SI unit of measurement of radioactivity.

Table 3 displays the clinical features of patients with and without SPM. The results indicated a significant variation in age at diagnosis of DTC. The two groups had no significant differences regarding gender, histological subtype, cumulative RAI activity, and follow-up period.

Table 3: Descriptive Analysis of Groups of DTC Patients with and without SPM

Baseline variables		With SPM (n=4)	Without SPM (n=496)	P value
Age at diagnosis of DTC (years)		49.3 (±12.7)	39.3 (±14.4)	0.17
Gender	Female	2 (50%)	407 (82.1%)	0.10
	Male	2 (50%)	89 (17.9%)	
Histological subtype (PTC)		4 (100%)	437 (88.1%)	0.47
Cumulative RAI (GBq)		3.35 (0.95)	3.45 (42.7)	0.55 / 0.001*
Follow-up period (years)		10.1 (8.3)	8.9 (10.8)	0.41

Values are represented by mean (±SD), number of patients (%), or median (range). DTC: differentiated thyroid cancer; SPM: second primary malignancy; RAI: radioactive iodine treatment; PTC: papillary thyroid cancer; GBq: The SI unit of measurement of radioactivity. *Statistically significant $p < 0.05$.

No incidences of SPM were observed in the 218 patients who received high doses of RAI

(≥ 3.7 GBq). Conversely, four cases of SPM were identified in the group receiving medium doses. The Mann-Whitney test, comparing cumulative RAI doses between the high-dose and SPM groups, yielded a significant p-value (<0.001).

Table 4 compares cumulative Radioactive Iodine (RAI) doses between patients who developed secondary primary malignancies (SPM) and the entire study population. It illustrates the distribution of RAI exposure within the cohort, highlighting a significant proportion of patients who received higher doses without developing SPM, suggesting a complex relationship between RAI dosage and SPM incidence.

Table 4: Compare Cumulative RAI Doses of Patients who Developed SPM to the Entire Population

Cumulative RAI (GBq)	Mean	Range
Entire population	5	(0.17-42.9)
patients with SPM	3.2	(2.57-3.53)

Discussion

The incidence of DTC is increasing worldwide, and as more DTC survivors are followed over a long period, concerns regarding the incidence of SPM in DTC survivors and its relationship with RAI treatment are growing. In this study, we evaluated DTC survivors over 11 years to investigate the incidence of SPM and its association with RAI treatment. We observed an incidence of 0.8% of SPM in our cohort of DTC survivors. Although RAI treatment was not significantly associated with SPM, there was a tendency towards a potential role of RAI exposure in anticipating the occurrence of SPM.

Previous studies have demonstrated that DTC survivors are at a greater risk of developing SPM than the general population [9]. The incidence of SPM in our cohort was found to be 0.8%, consistent with the previous studies conducted in different populations, which showed a similarly low incidence of SPM in thyroid cancer patients treated with RAI [10]. Previous studies have reported an increased risk of secondary malignancies in salivary glands, stomach, breast, central nervous system, colorectal, prostate, genitourinary tract, kidney, adrenal gland, bone and joints, soft tissue sarcoma, and hematological cancers among DTC survivors [11]. Our study only observed solid SPM in the breast, bladder, liver, and colon. The association between breast cancer and DTC has been previously reported [12].

There could be several reasons for the increased risk of secondary tumors in individuals who have survived DTC. These may include environmental and genetic factors, as some tumors have similar genetic traits as DTC. However, there is ongoing debate regarding the impact of RAI on this risk. The data regarding the association between RAI and secondary malignancies are inconsistent, and the effect may vary depending on the type of secondary tumor examined [12].

In this study, during a 9.5 (± 3) years follow-up, no significant correlation was detected between RAI treatment and the incidence of SPM in DTC survivors. This outcome is consistent with prior research, which has also reported no increase in overall SPM incidence associated with RAI [8]. This conclusion is based on several pieces of evidence. Firstly, the incidence of SPM was very low, and the small number of cases makes it difficult to establish a strong association. Secondly, the four patients who developed SPM had received RAI doses that were not significantly different, with a slightly lower median from those of other patients who did not develop SPM. The range of cumulative RAI doses among the entire study population was higher than that of the four patients who developed SPM. This indicates that the RAI dose was not related to the development of SPM, as many patients received higher doses than those four patients and did not develop SPM. These findings suggest that RAI treatment is not a significant risk factor for developing SPM.

Some studies found that patients receiving higher RAI doses are more likely to develop SPM [10]. Although we did not observe such a dose-dependent effect in our research, this may be attributed to the relatively small number of patients who experienced SPM. Furthermore, the overall cumulative RAI activity of the patients in our study was low, and research indicates that the risk of developing SPM is elevated in patients who received a cumulative RAI activity of over 40 GBq [10]. In our population, only one patient exceeded this dose.

In addition to RAI exposure, this research examined potential associations between SPM and demographic factors including age, gender, and follow-up period. However, statistical analysis did not yield significant findings attributed to the limited number of SPM cases observed within the study cohort. Despite the investigation into these variables, the study did not discern statistically significant correlations between age, gender, follow-up period, and the development of SPM, indicating the need for larger sample sizes or alternative methodologies to elucidate potential relationships.

Limitations

This study has some limitations that should be considered when interpreting the results. First, this study was a retrospective cohort study; therefore, it is impossible to determine a causeeffect relationship, and there is a chance of selection bias; hence the quality of the data was dependent on the accuracy and completeness of the medical records. Second, the sample size was relatively small, and the number of patients who developed SPM was low, which may limit the study's statistical power. Additionally, the study did not include active screening for secondary malignancies, and only clinically visible cases were identified, so the possibility of undiagnosed silent SPM should be considered. Finally, this study did not investigate other factors associated with the development of SPM, such as genetic, lifestyle, or environmental factors.

Conclusion

In conclusion, our study adds to the growing body of evidence on the risk and incidence of SPM in thyroid cancer survivors who underwent RAI treatment. This study investigated the incidence of SPM after RAI treatment among thyroid cancer patients in Oman. The findings suggest that age at diagnosis is an essential predictor of SPM occurrence. However, the incidence rate of SPM was low and unrelated to the RAI treatment dose. These findings suggest that RAI treatment is safe and does not significantly increase the risk of developing SPM.

Recommendations

Based on the findings of this study, we recommend that thyroid cancer patients who require RAI treatment should receive the treatment as per standard protocols, and the concern about SPM risk should not preclude the administration of the drug. However, clinicians should continue to monitor these patients for the development of SPM during follow-up. Furthermore, further studies with larger sample sizes and more extended follow-up periods are needed to confirm these findings and improve our understanding of the long-term effects of RAI treatment on

thyroid cancer patients.

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