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# SECOND MALIGNANCIES IN PATIENTS WITH DIFFERENTIATED THYROID CARCINOMA TREATED WITH LOW AND MEDIUM ACTIVITIES OF RADIOACTIVE I-131

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***Abstract***

***Background and aim.*** *This study aimed at determining whether there is a risk regarding the development of second primary malignancies after patient exposure to the low and medium radioiodine activity used during the treatment of differentiated thyroid cancers (DTC).*

***Methods.*** *Second primary malignancies that occurred after DTC were detected in 1,990 patients treated between 1970 and 2003. The mean long-term follow-up period was 182 months.*

***Results.*** *Radioiodine I-131was administrated at a mean dose of 63.2 mCi. There were 93 patients with at least one second primary malignancy. The relative risk of development of second malignancy in DTC patients was increased ($p<0.0001$) for breast, uterine and ovarian cancers compared with the general population.*

***Conclusions****. The overall risk concerning the development of second primary malignancies was related to the presence of DTC, but not to exposure to the low and medium activities of radioiodine administered as adjuvant therapy.*

**Keywords:** iodine radioisotopes; neoplasms, second primary, thyroid cancer

## Background

Differentiated thyroid cancers represent the most frequent endocrine tumors, with a 10-year overall survival rate of >90% [1,2]. In the management of these cancers radioiodine I-131 therapy (RIT) is used. The most controversial issues related to this therapy are its usefulness, mainly in low risk patients [1,3-8], and the most beneficial radiation dose for treatment [1-3,9]. During long-term follow-up patients treated with RIT may present with other primary malignancies. Findings reported in some previous studies have confirmed that there are risks related to radiation dose, age and latency [10-19]; however, there is both a lack of evidence and significant bias in demonstrating this relationship [20,21]. The aim of the present study was to investigate if there is a risk regarding the development of second primary malignancies after exposure to the low and medium radioiodine activities used during the treatment of differentiated thyroid cancers; a retrospective analysis was performed using a database from a tertiary cancer referral center.

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## Patients and methods

We retrospectively evaluated 1990 patients diagnosed with differentiated thyroid carcinoma (DTC) treated with thyroidectomy and adjuvant radioiodine therapy at the Institute of Oncology Cluj-Napoca between 1970 and 2003. All these patients were monitored and followed-up in the same department until 2013; the median surveillance interval was 182 months (range, 120–516 months). We obtained ethical approval for our study, and also patient informed consent regarding the use of their individual data. The patient group had a female/male ratio of 8:1, and a mean age of 47.2 years at the time of diagnosis of thyroid cancer. The disease stages of the patients were as follows: stage I, 51.7%; stage II, 19.6%; stage III, 17.5%; and stage IV, 11.2%. Radioiodine was administrated as adjuvant therapy to all patients. The mean radiation dose from I-131was 63.2 mCi (2338 MBq), with a range of 30 mCi (1111 MBq) to 90 mCi (3330 MBq); all patients treated with higher activities were excluded from the study. The overall survival rate was 94.7% at 10 years. Ninetythree patients were identified with at least one second primary malignancy, and 29 patients developed a second tumor after undergoing radioiodine therapy. The characteristics of the patient group are detailed in Table I.

### *Statistical methods*

Descriptive methods were employed for the analysis of the incidence of second primary malignancies, and the relative risk (RR) and odds ratio (OR) using the SPSS 17 statistical package. Student's t-test was used for comparing the groups. Differences were considered to be statistically significant at a p value $\leq 0.05$.

## Results

The present study focused on a cohort of 1990 patients with DTC treated and monitored in the same department from 1970-2003. All these patients received radical treatment, including the use of RIT; patients were only exposed to low and medium activities and were followed up for at least 10 years after RIT. Among this group, 93 patients presented with other primary tumors; one patient had two primary tumors associated with DTC (breast carcinoma and cervical carcinoma). A total of 64 patients presented with a primary tumor before the diagnosis of DTC, and were treated with RIT; 29 patients developed a second malignancy after DTC diagnosis and treatment with RIT. In the patients with a second malignancy the mean time interval between the two malignancies was 36±61.5 months. The type of tumors involved and their distribution are presented in Table II.

Because the patient group included an unusually high prevalence of females as compared with males (27:2), the pathologies of the second malignancies were strongly correlated with gender; the most frequently occurring pathology was breast carcinoma, followed by uterine and ovarian cancers. Data regarding the analysis of the RR and OR in the group of patients with DTC, and a previous malignancy that had occurred before RIT, are presented in Table III. The associated cancers were: breast; uterine, ovarian; lung; gastric carcinomas; malignant melanoma; leiomyosarcoma; basal cell carcinoma; neuroendocrine carcinoma; non-Hodgkin lymphoma; colorectal carcinoma; hepatocarcinoma; pancreatic adenocarcinoma; laryngeal cancer; esophageal cancer: seminoma; urinary bladder cancer; and metastases of unknown origin. The analysis concerning the RR and OR was only performed for the first eight cancer sites listed above, which were also present in the group of patients who developed a second malignancy after RIT. In the DTC patients a very strong correlation was found (p=0.0017) regarding the occurrence of breast carcinoma, uterine tumors, ovarian tumors(Table IV), as compared with the incidence of these neoplasms in the general population of the same region and country [22]. The single cancer where there was lack of correlation regarding the RR and OR was basal cell carcinoma (p=0.3516 and p=0.3517, respectively).

In Table V the comparative RR and OR for the low and medium dose RIT groups are presented; the data emphasize the lack of correlation regarding the occurrence of lung and gastric cancers in the DTC patients after treatment with RIT.

In Table VI the results of the analysis using Student's t-test concerning the comparison of the two groups of patients with second malignancies, which developed before and after the use of low and medium activities of radioiodine, are presented. It was conclude from this analysis that there was no correlation between the occurrence of second malignancies and the dose of radioiodine used (p=0.6228).

**Table I.** Characteristics of the patient study group.

| | Cases of DTC radiated with low and medium I-131 1970-2003 | Cases with DTC and other primary malignancy developed before RIT | Cases with DTC and second primary malignancy developed after RIT |
|---|---|---|---|
| **NUMBER** | 1990 | 64 | 29 |
| **GENDER** | | | |
| Female | 1768 | 55 | 27 |
| Male | 222 | 9 | 2 |
| **AGE (YEARS)** | | | |
| Mean (+/-SD) | 47.2 (+/- 28.1) | 52.2 (+/-14.7) | 50 (+/-9.93) |
| **HISTOLOGY** | | | |
| Papillary DTC | 1804 | 57 | 22 |
| Follicular DTC | 186 | 7 | 7 |
| **STAGES (%)** | | | |
| I | 51.7 | 54.2 | 55.2 |
| II | 19.6 | 12.6 | 6.9 |
| III | 17.5 | 21.4 | 24.1 |
| IV | 11.2 | 11.8 | 13.8 |
| **RADIOIODINE** | | | |
| I-131 (mCi) Mean (+/- SD) | 63.3 (+/- 21.7) | 69.1 (+/-31.1) | 69.2 (+/-30.6) |

| **INTERVAL (months)** | *Before* DTC and RIT | *After* DTC and RIT |
|---|---|---|
| Min | 0 | 12 |
| Max | 432 | 204 |
| Mean (+/- SD) | 44.2 (+/-78.9) | 36 (+/-61.5) |

**Table II.** Second primary malignancies in patients with differentiated thyroid carcinoma (DTC) who underwent radioiodine therapy (RIT).

| TUMOR TYPE | SECOND PRIMARY MALIGNANCY *before* DTC and RIT (number of patients) | SECOND PRIMARY MALIGNANCY *after* DTC and RIT (number of patients) |
|---|---|---|
| Breast cancer | 19 | 14 |
| Uterine cancer | 12 | 7 |
| Ovarian cancer | 3 | 3 |
| Lung cancer | 3 | 1 |
| Malignant melanoma | 3 | 1 |
| Gastric cancer | 1 | 1 |
| Leiomyosarcoma | 0 | 1 |
| Basal cell carcinoma | 2 | 1 |
| Lymphoma | 4 | 0 |
| Colorectal carcinoma | 5 | 0 |
| Hepatocarcinoma | 1 | 0 |
| Pancreatic carcinoma | 1 | 0 |
| Larynx cancer | 2 | 0 |
| Esophagus cancer | 1 | 0 |
| Seminoma | 1 | 0 |
| Neuroendocrine cancer | 1 | 0 |
| Urinary bladder | 1 | 0 |
| Unknown origin metastases | 4 | 0 |

**Table III.** Relative risk (RR) and odds ratio (OR) regarding the occurrence of second malignancies in patients with differentiated thyroid carcinoma (DTC) *before* treatment with radioiodine therapy (RIT).

| | Incidence in general population Number of cases/100.000 inhabitants in Romania* | Second primary malignancy *before* DTC and RIT (number of patients) | Relative Risk (RR) for second malignancy in DTC *before* RIT | P statistic significant (p<0.05) | Odds ratio (OR) | P statistically significant (p<0.05) |
|---|---|---|---|---|---|---|
| Breast Cancer | 66.2 | 19 | 14.4 (95%CI 8.6 – 23.95) | p<0.0001 | 15.5 (95% CI 8.7 -24.2) | p< 0.0001 |
| Uterine cancer | 35 | 12 | 17.22 (95% CI 8.9-33.1) | p< 0.0001 | 17.3 (95% CI 8.9-33.4) | p< 0.0001 |
| Ovarian cancer | 13.6 | 3 | 10.78 (95%CI 3.09-37.4) | p= 0.0002 | 10.78 (05%CI 3.09-37.5) | p= 0.0002 |
| Lung cancer | 15.8 | 3 | 9.42 (95%CI 2.74-32.3) | p=0.0004 | 9.43 (95%CI 2.74-32.4) | p=0.0004 |
| Gastric Cancer | 8.5 | 2 | 11.16 (95%CI 24-51.6) | p=0.002 | 11.17 (95%CI 24-51.17) | p=0.002 |
| Mal melanoma | 4.5 | 3 | 83.75 (95%CI 20-3502) | p<0.0001 | 30.2 (95%CI 7.2-126) | p<0.0001 |
| Leiomyosarcoma | 0.1 | 0 | 167.4 (95%CI 6.8-4108) | p=0.0017 | 167.4 (95%CI 6.8-4112) | p-0.0017 |
| Basocellular cc | 128 | 1 | 0.39 (95%CI 0.05-2.8) | p=0.3516 | 0.39 (95%CI 0.05-2.8) | p=0.3514 |

*-EUCAN statistics for cancers [22]

**Table IV.** Relative risk (RR) and odds ratio (OR) regarding the occurrence of second malignancies in patients with differentiated thyroid carcinoma (DTC) *after* treatment with radioiodine therapy (RIT).

| | Incidence in general population Number of cases/100.000 inhabitants in Romania* | Second primary malignancy *after* DTC and RIT (number of patients) | Relative Risk (RR) for second malignancy in DTC *after* RIT | P statistic significant (p<0.05) | Odds ratio (OR) | P statistically significant (p<0.05) |
|---|---|---|---|---|---|---|
| Breast Cancer | 66.2 | 14 | 10.6 (95%CI 5.9 - 18.9) | p<0.0001 | 10.7 (95% CI 6.0 -19.1) | p< 0.0001 |
| Uterine cancer | 35 | 7 | 10.05 (95% CI 4.4-22.5) | p< 0.0001 | 10.08 (95% CI 4.2-22.7) | p< 0.0001 |
| Ovarian cancer | 13.6 | 3 | 10.7 (95%CI 3.09-37.4) | p< 0.0002 | 10.7 (05%CI 3.09-37.5) | p< 0.0002 |
| Lung cancer | 15.8 | 1 | 3.1 (95%CI 0.4-23.6) | p=0.2668 | 3.1 (95%CI 0.4-23.7) | p=0.2669 |
| Gastric Cancer | 8.5 | 1 | 5.5 (95%CI 0.7-44.1) | p=0.1027 | 5.5 (95%CI 0.7-44.1) | p=0.1028 |
| Mal. melanoma | 4.5 | 1 | 10.05 (95%CI 1.1-85.9) | p=0.0351 | 10.05 (95%CI 1.1-86.1) | p=0.0351 |
| Leiomyosarcoma | 0.1 | 1 | 150.6 (95%CI 6.1-3697) | p=0.021 | 150.7 (95%CI 9.1-3702 | p=0.0211 |
| Basocellular cc. | 128 | 1 | 0.39 (95%CI 0.05-2.8) | p=0.3516 | 0.39 (95%CI 0.05-2.8) | p=0.3514 |

*-EUCAN statistics for cancers [22]

**Table V.** Comparative probability of the occurrence of second malignancies in the low and medium dose RIT groups.

| TYPE OF CANCER | Second primary malignancy *before* DTC and RIT | | Second primary malignancy *after* DTC and RIT | |
|---|---|---|---|---|
| | RR | OR | RR | OR |
| Breast Cancer | p<0.0001 | p< 0.0001 | p<0.0001 | p< 0.0001 |
| Uterine cancer | p< 0.0001 | p< 0.0001 | p< 0.0001 | p< 0.0001 |
| Ovarian cancer | p= 0.0002 | p= 0.0002 | p< 0.0002 | p< 0.0002 |
| Lung cancer | p=0.0004 | p=0.0004 | *p=0.2668* | *p=0.2669* |
| Gastric Cancer | p=0.002 | p=0.002 | *p=0.1027* | *p=0.1028* |
| Mal. melanoma | p<0.0001 | p<0.0001 | p=0.0351 | p=0.0351 |
| Leiomyosarcoma | p-0.0017 | p-0.0017 | p=0.021 | p=0.0211 |

**Table VI.** Student t-test applied to the two groups of patients (treated with low and medium dose radioiodine therapy with differentiated thyroid carcinoma (DTC) and second malignancies, *before* and *after* RIT.

| | **Mean** | **Standard deviation** | **Standard error** | **p*** |
|---|---|---|---|---|
| Group 1 (After RIT) | 5.2 | 5.29 | 2.45 | *p=0.6228* |
| Group 2 (Before RIT) | 7.4 | 7.89 | 3.52 | |

* p<0.05 – statistically significant

## Discussion

DTC represents one of the most rapidly increasing neoplastic pathologies, a fact that imposes a requirement for a clear strategy for the establishment of precise diagnostic and interventional procedures. As a result of high survival rates at follow-up times of 10-20 years and rare aggressive outcomes, DTC treatment necessitates less harmful strategies to achieve the best patient quality of life. In this regard, the recent guidelines recommend a more conservative treatment approach (mainly related to low risk carcinomas) that avoids unnecessary radiation exposure using radioiodine therapy [23]; determination of the lowest most efficient dose is one of the key goals. In our more recent history there has been appreciable evidence underlining the role, played by ionizing radiation in the development of cancer; for example the malignant lesions that occurred as a result of the radiation fallout in Japan during the Second World War, and after the Chernobyl nuclear reactor accident among others. Accordingly, special attention is given to the potential development of cancer after irradiation, mainly in the case of thyroid cancers where the survival rates are high and the monitoring intervals extend over decades [24].

The RR and OR for the group of patients with DTC who developed a second tumor after RIT showed a statistically significant correlation for breast carcinoma (p<0.0001), uterine (p<0.0001) and ovarian cancers (p=0.0002), malignant melanoma (p=0.0351) and leiomyosarcoma (p=0.0021); however, there was no correlation regarding lung cancer (p=0.266) and gastric cancer (p=0.1027). It is interesting that even if lung carcinoma was the second most frequent tumor for both sexes in the region of reference, change in the incidence of this cancer in the patient groups after RIT was not significant.

Many studies have already published data about the role of radioiodine in the development of second malignancies [10,12,21], but the present study refers to the analysis of low and medium activities, where the results show no correlation between the occurrence of second malignancies and the use of radioiodine (p=0.6228). These results might be an argument for trying to promote in daily practice, the use of lowest effective radioiodine dose and to have an individualized approach of each patient.

The analysis performed in the current study indicated that the occurrence of a second primary malignancy was strongly correlated with the presence of DTC, and was not caused by radiation carcinogenesis as a result of RIT. Considering that the most frequent pathologies were breast, uterine and ovarian cancers, the development of secondary primary cancers might be linked with endocrine and genetic predispositions, fact that requires further studies

and researches.

## Conclusions

The overall risk regarding the development of second primary malignancies was found to be related to the presence of thyroid cancer, and had no correlation with the low and medium activities of radioiodine administered as adjuvant therapy for differentiated thyroid cancers (p=0.6228). The occurrence of breast, uterine and ovarian cancers as secondary malignancies requires further research to find possible correlations regarding the influence of the endocrine system.

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