Topic: **SECOND PRIMARY TUMORS IN PATIENTS WITH DTC**

Title: The incidence of second primary tumors in thyroid cancer patients is increased, but not related to treatment of thyroid cancer.

Authors: **Verkooijen RB, Smit JW, Romijn JA, Stokkel MP (Leiden, The Netherlands)**

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SUMMARY

Objective: The aim of the present study was to assess the prevalence of second primary tumors in patients treated for thyroid cancer. Furthermore, the authors wanted to assess the standardized risk rates for all second primary tumors, but especially for breast cancer, as data in the literature have indicated an excessive risk in differentiated thyroid cancer (DTC) patients for this tumor.

Material & Methods: Consecutive patients (n=282) were included, who had received ablation treatment with I-131 at the Leiden Medical Center (between January 1985 & December 1999). The mean period of follow-up was 10.6 ± 4.1 years.

Results: Thirty-five of the 282 patients (12.4%) had a second primary tumor (SPT), either preceding or following the diagnosis of thyroid cancer. Five other patients had three primary tumors, including DTC. As a result, 40 additional tumors were found in this group, revealing an overall prevalence of 14.2%. Twenty tumors (7.1%) preceded the thyroid cancer with a mean interval of 5.7 years (range: 0.5-22.0 years), whereas 20 tumors (7.1%) occurred after this tumor with a mean interval of 6.7 years (range: 1.0-15.0 years). In 13 female patients, breast cancer was found as SPT. The standardized incidence rate (SIR) for all cancers after the diagnosis of DTC in this study population was not increased (SIR: 1.13; C.I.: 0.68-1.69). There was, however, an increased SIR for all cancers either following or preceding DTC (SIR: 2.26; C.I.: 1.60-3.03), and this increased SIR was mainly caused by breast cancer (SIR: 3.95; C.I.: 2.06-6.45).

Conclusion: Patients with DTC have an overall increased standardized incidence rate for second primary tumors, but not for second primary tumors following I-131 therapy. These findings suggest a common etiologic and/or genetic mechanism to explain the increased risk of having more than one tumor, instead of a causal relation.

COMMENT

Differentiated thyroid cancer (DTC) accounts for approximately 0.5-1.5% of all malignancies. Some studies have found a relationship between I-131 administration and the occurrence of secondary cancers (bone, soft tissue, colorectal, salivary glands, etc.). Other studies have reported an increased incidence of breast and kidney cancers among women treated for DTC, although the increased incidence was unrelated to exposure to I-131.

Present results indicate that I-131 therapy is not associated with an increased incidence of malignancies following treatment of DTC. Present results also indicate that there is an increased incidence of second primary tumors (especially breast cancer) in patients with DTC. The authors speculate that genetic predisposition and probably environmental factors seem to be a better explanation for the double occurrence, as at least half of the breast tumors appeared before treatment of DTC with I-131. Even though the mean follow-up period was relatively long (over ten years), one obvious limitation of the study was the relatively small number of patients included in the database.

Recently, a large multi-national study was published of second primary cancers in patients with thyroid cancer (Sandeep *et al*; JCEM 91:1819-181825, 2006). It was conducted in 13 population-based cancer registries and included 39.000 patients with primary thyroid cancer. In that study, 2.821 second primary tumors (SPT) were observed, yielding an overall standardized incidence rate (SIR) of 1.31. Increased incidence rates were found for cancers of the oral cavity (SIR: 1.43), small intestine (SIR: 2.11), bone (SIR: 3.62), soft tissue sarcoma (SIR: 3.63), kidney (SIR: 2.33), endocrine glands (SIR: 6.75), lymphoma (SIR: 1.68), and leukemias (SIR: 2.26). Surprisingly, the SIR for breast cancer was 1.31, i.e. much lower than in present study. Conversely, the study of Sandeep *et al* also showed that the risk of thyroid cancer as a second primary tumor was also increased in patients who primarily had other cancers (lung, larynx, oesophagus, salivary glands).

The conclusion is that clinicians should maintain a high index of suspicion during follow-up, both for SPT following treatment for thyroid cancer and for cancer of the thyroid as SPT.

(***Daniel Glinoer, M.D.; Ph.D.***)

See Table below

Table 2 Locations of second primary tumors in differentiated thyroid cancer (DTC) patients.

Tumors preceding DTC	*n*	Mean cumulative I-131 activity (MBq)	Mean interval (years) (range)	Tumors following DTC	*n*	Mean cumulative I-131 activity (MBq)	Mean interval (years) (range)
Melanoma	2	22 400	13 (4–22)	Melanoma	1	1850	1
Breast	8	4900	4.3 (2–10)	Breast	5	9000	6.6 (2–11)
Colon	2	9100	3.3 (0.5–6)	Cervix uteri	2	5050	4 (1–7)
Lung	2	8400	2.3 (0.5–4)	Ovary	2	2400	8.5 (2–15)
Adrenal	1	8900	15	Endometrium	1	16 512	7
Salivary gland	1	2800	17	Pancreas	2	2800	7 (3–11)
Grawitz tumor	1	7400	7	Bladder	1	2800	3
Stomach	1	24 735	2	Lung	1	2800	14
Prostate	1	26 740	2	Prostate	1	9400	1
Lymphoma	1	15 725	0.5	Hepatocellular	1	15 400	2
				Grawitz	1	21 100	14
				Leukemia	1	2800	8
				Lymphoma	1	2800	12
Overall	20		5.7 (0.5–22)	Overall	20		6.7 (1–15)

SPT, second primary tumor.