

# Pattern of second primary malignancies in thyroid cancer patients

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## Abstract

Many factors, including relatively young age of thyroid cancer diagnoses and improved survival, have led to increased concerns about the occurrence of second primary malignancies. This paper describes the pattern of occurrence of second primary malignancies in patients who were treated for malignant thyroid neoplasms in an Indian hospital. There were 21 affected patients of the approximately 4500 seen over 25 years. Most of the second primary cancers are solid tumors, and when nonthyroid cancers are the second tumors, ductal carcinoma of the female breast is the most common. Most of these tumors have very short detection intervals (including synchronous occurrences), suggesting that therapy with internal radiation was not contributory to the tumor development. When thyroid malignancies were the second primary cancers, they usually follow radiotherapy to the head and neck region for treatment of the first primary tumor and tend to be of aggressive histologic types than the common well differentiated thyroid carcinomas.

**Key words:** Radiation, radiotherapy, second malignancies, thyroid cancer

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## Introduction

Improved early detection of first malignancies and availability of more effective treatment modalities have resulted in prolonged survival, with consequent increased risk of secondary malignancies.<sup>[1]</sup> Also increasing incidence, improved prognosis and the relatively young age at thyroid cancer diagnoses coupled with the employment of radioiodine in diagnostic and therapeutic doses have led to concerns about the development of second primary malignancies in thyroid cancer patients. Thyroid cancers have been known to result in patients exposed early in life to radiation from radiotherapy. In addition, they have also been known to arise as second primary malignancies after other cancers. Some organs concentrate radioiodine, e.g., salivary gland, colon and bladder<sup>[2-4]</sup> while others, e.g., breast tissue<sup>[5]</sup> express sodium iodide symporter, a membrane glycoprotein important in

the active transport of iodide (including radioactive iodide) in the thyroid gland. This potentially exposes these organs to significant radiation and the attendant risk of radiation-induced malignant transformations. Other studies suggest a common genetic predisposition to explain the associations<sup>[6]</sup> of thyroid carcinomas and other identified comalignancies. This paper describes the pattern of second primary malignancies in affected patients of the 4500 patients treated for thyroid carcinoma at the All India Institute of Medical Sciences within the past 25 years. All patients already had thyroidectomies ranging from hemi-thyroidectomy to total thyroidectomy. Radioiodine-131, in diagnostic and therapeutic doses was also given to all patients according to institutional protocols.

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## Materials and Methods

A retrospective search through 4500 case notes of patients seen at the nuclear thyroidology clinic of the All India Institute of Medical Sciences within the past 25 years yielded 21 patients (0.45%) with second primary malignancies. All but three cases had thyroid carcinoma as the first primary cancer. The variables analyzed included age (at presentation for the second malignancy), sex, past history of external beam radiotherapy in childhood or youth especially to the head and neck, and thyroid cancer presentation. Other variables analyzed include the histology of the thyroid lesion, immediate past history of external beam radiotherapy, presence or absence of metastasis of thyroid cancer and finally the site of second primary neoplasm. The synchronous or metachronous occurrence of the second primary malignancies as well as their detection intervals between the first and the second malignancies were also analyzed.

## Results

There were a total of 21 patients with second malignancies discovered in the search, representing 0.45% of the approximately 4500 cases [Table 1]. Of these 11 (52.4%) were females while 10 (47.6%) were males (that is a female to male of 1.1:1). The mean age was 49.3 years. Females were found to be older at presentation with a mean age of 52.5 years compared to 45.8 years found in men. A total of 18 out of our 21 patients presented with thyroid cancer

as the first malignancy. The rest three patients had thyroid cancer as a second primary malignancy. The histopathology from the thyroidectomy specimens among those with thyroid carcinoma as the first primary malignancy showed that 12 patients or 66.7% had papillary thyroid cancer, 3 (16.7%) had follicular variant of papillary thyroid cancer (FVPTC), while 3 (16.7%) had follicular carcinoma of the thyroid. As mentioned earlier, three patients had a reverse situation where thyroid carcinomas were discovered down the line after the patients had been diagnosed and treated for other malignancies. All three had received external beam radiotherapy (EBRT) to the head and neck region as part of the treatments for their first cancers. In this group of patients, the second primary thyroid cancers consisted each of follicular carcinoma of thyroid (FCT) with Hurthle cells, papillary cancer thyroid (PCT) and insular cell carcinoma. Hurthle and insular cell cancers are aggressive malignancies and these represented 2 of the 3 tumors.

Among the 18 patients who had thyroid cancer as first malignancies, of which 17 are solid tumors and one a leukemia (CML), about 16.7% of malignancies occurred in the region of the head and neck, specifically one each for tongue, lip, and eye.

In 5 patients out of these 18 patients, there was synchronous detection of co-malignancies. When considered as a group, patients with short T1T2 intervals of 3 years and less (including synchronous tumors, T1T2 = 0) were 13/18 (72.2%) and has a mean T1T2 interval of 0.8 years.

**Table 1: Distribution of first and second primary tumors**

Age (years)	Sex	2 <sup>nd</sup> Primary Ca (T2)	Age at first presentation (yrs)	1 <sup>st</sup> Primary Ca (T1)	T1T2 interval (years)
48	F	Inv D. Ca, breast	45	PCT	3
35	F	Inv D. Ca, breast	19	PCT	14
39	M	FCT with Hurtle Cells	8	HD	31
46	F	Ca tongue	46	PCT	0 <sup>#</sup>
30	M	CML	16	PCT	14
46	F	Chondrosarcoma of Femur	45	PCT	1
55	F	PCT	48	Inv D. Ca, breast	7
50	F	Inv D. Ca, breast	50	FVPCT	0 <sup>#</sup>
59	M	Adenocarcinoma of Rectum	51	PCT	8
50	M	Adenocarcinoma of Lungs	42	PCT	8
48	F	Inv D. Ca, breast	48	FCT	0 <sup>#</sup>
35	F	Inv D. Ca, breast	34	PCT	1
52	F	Ca ovary	51	FCT	1
55	M	Renal cell Ca	47	PCT	8
78	M	Squamous cell Ca, lip	78	PCT	0 <sup>#</sup>
65	F	Malignant melanoma of eye	64	FVPCT	1
36	M	Insular cell Ca, thyroid	17	Ca larynx	19
67	M	Ca prostate	66	FCT	1
60	F	Phylloides tumor, breast	60	FVPCT	0 <sup>#</sup>
38	F	Inv D. Ca, breast	37	PCT	1
44	M	HD	43	PCT	1

HD=Hodgkin's disease; FCT=Follicular cancer of the thyroid; FVPCT=Follicular variant of papillary cancer of the thyroid; PCT=Papillary cancer of the thyroid; Ca=Carcinoma; Inv D. Ca=invasive ductal carcinoma; <sup>#</sup>=synchronous tumor

The rest (5/18) had T1T2 of 8 years and above, with a mean of 10.3 years.

In all these 18 patients, malignancies of the breast (including phylloides tumor) were the commonest, accounting for 7 (38.9%). All were female breast tumors. When only females are considered, the breast tumors made up 7/11 (63.6%) of cases.

## Discussion

Though they occur and are to be kept in mind by oncologists, second primary malignancies in thyroid cancer patients cannot be said to be frequent. In this study, about 0.45% of the patients had a second primary malignancy. Most of the malignancies occurring in association with thyroid cancers in this study are solid tumors; all cases but one being so; the exception is the single case of chronic myeloid leukaemia. Thyroid cancers are treated mainly with internal radiation. It has been recognized that radiotherapy induces mostly solid tumors and that the risk of leukemia following radiation is considerably smaller than after chemotherapy.<sup>[1]</sup> Breast cancer associated with female thyroid cancer appears to be of concern judging from this series where seven of such cases were seen. Many studies evaluating the risk of breast cancer following thyroid cancer have generally found a significant but modest (20-30%) overall increased risk.<sup>[6-14]</sup> Other studies have found that this increased risk is higher in younger thyroid cancer patients<sup>[6,8,9,11]</sup> and that itrogenic effects do not appear to explain these associations.<sup>[7,8,10,11]</sup> In one of our patients there was a 7-year interval between the discovery and treatment of a breast cancer and the subsequent discovery of a second cancer in the thyroid gland. However, in most of the affected patients, thyroid and breast cancers were either synchronously detected or detected within three years. In carcinogenesis, this interval is too short for one to even begin to look at the therapeutic radiation as being of etiologic significance.

As earlier stated, three patients in our study (two males and one female) presented with an initial non-thyroid malignancy. Later on they were diagnosed with thyroid cancer. One thing common to these patients is that they had all received adjuvant external beam radiotherapy to the head and neck region as part of the treatments for their first cancers (Hodgkin's lymphoma, laryngeal carcinoma, and breast cancer, respectively). These cases appear to suggest that radiation in the form of external beam radiotherapy (EBRT) had some role in the initiation of their thyroid cancers. A study<sup>[11]</sup> found that ten of twenty patients with a history of receiving EBRT to the head and neck region later on developed thyroid malignancy. Radiation-induced thyroid neoplasia in children is a recognized result of direct irradiation to the thyroid as seen in treatments for Hodgkin's disease.<sup>[15,16]</sup> Apart from finding thyroid cancer in this group of patients, the tumors were mostly of aggressive types. In

addition these patients had peculiarly long T1T2 times (31 and 19 years respectively). Though we are cautious (due to our small sample size) in reaching a conclusion concerning the role of head and neck EBRT in the initiation of aggressive thyroid cancer histologies, this result however agrees with similar ones which concluded that EBRT to the head and neck in the younger age group<sup>[17]</sup> increases the risk of thyroid carcinomas. Again it appears that the males within this subset had much longer T1T2 times compared to the lone female. Again the small sample size prevents any conclusions concerning the influence of patient's gender on T1T2 times.

For over half a century, radioiodine (<sup>131</sup>I) has been used in the diagnosis and treatment of patients with papillary and follicular thyroid carcinoma.<sup>[7]</sup> With respect to the risk of development of second primary cancers in adult patients in whom radioiodine <sup>131</sup>I has been used in diagnostic doses<sup>[18]</sup> as well as in the treatment of benign thyroid conditions like hyperthyroidism,<sup>[19,20]</sup> much larger doses are deployed in the treatment of thyroid malignancies, e.g., follicular and papillary thyroid cancers of the thyroid. This has consequently resulted in significant patient radiation exposure.<sup>[7]</sup> Paradoxically, among other cancers differentiated thyroid carcinomas present a relatively benign biology, resulting in long life expectancy. It is feared that this may allow sufficient time for the patient to develop another cancer at another site.<sup>[21]</sup> To buttress this, an autopsy series found that 50% of patients who had thyroid cancer were discovered to have another entirely separate cancer.<sup>[22]</sup>

Apart from the fact that sodium iodide symporter (a membrane glycoprotein that mediates active iodide transport in the thyroid) finds extrathyroidal expression in places like the salivary gland, stomach and breast, ingested radioiodine used in the treatment of thyroid cancer is eliminated from the body via the faeces in the digestive tracts, in saliva and urine. Minor excretion occurs through sweat. These pathways potentially expose the related organs to ionizing radiation,<sup>[23]</sup> which may possibly initiate carcinogenesis at these sites. Even so the association, for example, between the renal excretion of radioiodine and kidney cancers has received less attention.<sup>[24]</sup> In this study, we found only one case of renal cancer and one case of prostatic cancer as second malignancies in patients with thyroid carcinoma and treated with radioiodine. Some workers consistently report a substantial increased risk of two or more fold for kidney cancer following thyroid cancer.<sup>[7,11,12,25]</sup> In one follow-up study on 2968 people with thyroid cancer, an increase in kidney, endocrine, and nervous system tumors was found.<sup>[26]</sup> Also the increased risk of second primary kidney cancer has been shown previously in population based studies,<sup>[27]</sup> but does not appear to be related to <sup>131</sup>I exposure.<sup>[7]</sup> A recent study<sup>[28]</sup> has identified a familial association between papillary thyroid cancer and papillary renal neoplasia. A mutant susceptibility

gene designated as *FPTC/PRN* has been implicated. We found two cases of second malignancies involving the gastrointestinal system. One patient had cancer of the tongue while the other had cancer of the rectum.

## Conclusion

The occurrence of other malignancies with thyroid carcinoma in patients remains an important thing to bear in mind and therefore patients should be adequately screened. Second malignancies in thyroid cancer patients, though not frequent, is important to note. Female breast carcinoma is the highest occurrence in this study, this is significant since there is only a slight preponderance of females among the cases. When thyroid carcinoma is the first to be diagnosed, the second primaries do not appear to be often related with the radioiodine therapy given for the treatment of the thyroid tumors as the interval between diagnoses is usually too short for *de novo* tumorigenesis. In contrast, when thyroid carcinomas are the second primary tumors, they appear to be causally related to the treatment given for the first primary malignancies and they tend to be of aggressive types. As in all disease conditions early detection may provide the hope of a better outcome for such patients. Therefore the need for extended surveillance among patients who had received EBRT to the head and neck regions as treatment for a first cancer cannot be overemphasized.

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