

**Aim of the study:** Primary squamous cell carcinoma (SCC) of the thyroid gland is extremely rare. Infrequently, primary SCC of the thyroid gland is accompanied by other thyroid diseases such as Hashimoto's thyroiditis (HT). Recently, studies have demonstrated that differentiated thyroid cancer with coexisting HT has a better prognosis. However, the prognosis of patients with primary SCC of the thyroid gland and coexistent HT has not been clearly identified. We compared the clinical characteristics and disease stages of patients with primary SCC with and without lymphocytic thyroiditis (LT).

**Material and methods:** We reviewed reports of primary SCC of the thyroid gland published in the English literature.

**Results and conclusions:** We identified 46 papers that included 17 cases of primary SCC of the thyroid gland with LT and 77 cases of primary SCC of the thyroid gland without LT. Lymph node metastasis and local invasion rates did not differ between these two groups. Distant metastases were absent in patients with LT, and were observed in 13 (16.9%) patients without LT. A greater proportion of patients without LT had advanced stage disease (stage IV A-B-C) than patients with LT ( $p < 0.05$ ). Patients with primary SCC of the thyroid gland and coexisting LT had lower tumour-node-metastasis stage and frequency of distant metastasis than those without LT. Lymphocytic infiltration in patients with SCC appears to limit tumour growth and distant metastases.

**Key words:** Hashimoto's thyroiditis, primary squamous cell carcinoma, thyroid gland, tumour aggressiveness.

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# Less aggressive disease in patients with primary squamous cell carcinomas of the thyroid gland and coexisting lymphocytic thyroiditis

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## Introduction

According to the published literature, primary differentiated thyroid carcinomas are the most common causes of thyroid malignancies. Besides these differentiated thyroid malignancies, other rare primary thyroid malignancies such as primary squamous cell carcinoma (SCC), osteosarcoma, and lymphoma have been reported [1–3].

Primary SCC of the thyroid gland is a rare malignancy that is usually secondary to metastasis from an SCC of the upper aerodigestive tract. Squamous cell carcinoma constitutes < 1% of all thyroid malignancies [1]. The disease usually affects older patients in their fifth to sixth decade of life. Most patients present with an enlarged mass in the neck, with or without pain, and cervical lymphadenopathy. Infrequently, primary SCC of the thyroid gland is associated with other thyroid diseases such as Hashimoto's thyroiditis (HT), papillary, medullary, follicular, and anaplastic thyroid carcinomas. Usually HT is related to malignancies such as lymphomas, but it can also be related to follicular, papillary, and medullary thyroid carcinomas. Primary SCC on the other hand is rarely encountered with HT [4–19].

Recently, studies have demonstrated that patients with differentiated thyroid cancer and coexisting HT have a better prognosis than those without HT [20]. However, the prognosis of patients with primary SCC of the thyroid gland and coexisting HT has not been clearly identified.

We performed a literature review of primary SCC patients with and without HT to determine the influence of coexisting HT on the outcomes of patients with primary SCC.

## Material and methods

### Literature search

A literature search was performed of the PubMed and Google databases using the following terms in various combinations: primary SCC of the thyroid gland and HT. After an assessment of the abstracts, all relevant full-text

papers published in English were accessed. Case reports were divided into two groups depending on the presence or absence of LT. Age, sex, lymph node metastasis, local invasion, distant metastasis, treatment modality, immunohistochemical markers, and the tumour-node-metastasis (TNM) stage were assessed. We determined the TNM stage based on the AJCC TNM staging system in patients with undefined TNM stage [21].

We excluded cases of SCC combined with other thyroid malignancies such as adenocarcinoma, anaplastic carcinoma, or papillary carcinoma. We also excluded reports including more than one case that was undistinguished, regardless of the presence or absence of LT.

### Statistical analysis

SPSS software (Version 19.0, IBM, Chicago, IL, USA) was used for the statistical analyses, and a  $p$  value of  $< 0.05$  was considered statistically significant. The values are expressed as mean  $\pm$  SD. Differences between the groups were evaluated by the Mann-Whitney  $U$  test and  $\chi^2$  test.

### Results

A total of 88 trial titles and abstracts were identified using the initial search criteria. Applying the above criteria, we could only access 46 full papers written in English: 16

and 77 cases with primary SCC of the thyroid gland with and without LT, respectively, determined by pathological examination of specimens. Our patient who was diagnosed with primary SCC of the thyroid gland and coexisting HT was added to the group with HT during the statistical analysis (unpublished data). Criteria for identifying patients with LT are shown in Table 1.

The mean age of the patients with and without LT was  $57.24 \pm 15.49$  and  $61.61 \pm 13.31$  years, respectively. Tumour size with and without LT was  $4.61 \pm 2.81$  and  $5.19 \pm 3.14$  cm, respectively. Tumour size, age, sex, lymph node metastasis, and local invasion did not differ between groups ( $p > 0.05$ ). No distant metastases were noted in patients with LT, whereas 13 (16.9%) patients without LT had distant metastases. The most common metastatic region was the lung (76.9%). Less common regions included the liver, bones, heart, and kidneys. Patients without LT had more advanced disease stages (stage III–IV A-B-C) than patients with LT ( $p < 0.05$ ). The clinical and general characteristics of the groups and TNM stages for both groups are shown in Table 2. We could not compare the survival rates of the two groups because some patients were alive at the time the manuscript was written.

Whole group analyses were performed. Fine-needle aspiration biopsy (FNAB) was performed for 42 of 94 patients. Squamous cell carcinoma was preoperatively diagnosed

**Table 1.** General features of patients with lymphocytic thyroiditis

Author (case no.), [ref]	Gender/age (yr)	Tumour size (cm)	Treatment	TNM stage	Survival (month)	Immunohistochemistry
Shrestha <i>et al.</i> [4]	F/75	–	TT, RT	T4aN0M0	31	TTF1, CK5/6, CK7, CK903 (+); Tg (–); Ki67 30%, p53 30%
Tunio <i>et al.</i> [5]	F/54	10	RT	T4N0M0	5 <sup>a</sup>	
Sanchez-Sosa <i>et al.</i> [6]	F/13	2.3	TT	T2N0M0	2 <sup>a</sup>	CK7, CKAE1/AE3 (+); TTF1, Tg (–); Ki67 30%, P53 30%
Chaudhary <i>et al.</i> [7]	F/76	2.5	TT, RT	T4N1M0	12	
Korovin <i>et al.</i> (2) [8]	F/48	–	STT	T4NxM0	9	
Sahoo <i>et al.</i> (1) [9]	F/42	3	STT	T2N1M0	6	
Chintamani (1) [10]	F/50	3	PT, RT	T4N1M0	7	
Kondo <i>et al.</i> [11]	F/61	2.7	TT, RT	T2N0M0	34 <sup>a</sup>	TTF1 (–); Ki67 74%, p53 60%
Ab Hadi <i>et al.</i> [12]	F/60	3	TT, RT	T2N0M0	–	CK (+)
Batchelor <i>et al.</i> [13]	F/75	–	TT, RT	T4N0M0	15	CK903, CK5/6, TTF1 (+); Tg (–); Ki67 30%, P53 30%
Long <i>et al.</i> [14]	M/57	4.5	TT, RT, CT	T3N1M0	12	
Harada <i>et al.</i> (2) [15]	F/63	8	PT, RT, CT	T4N1M0	14	
Huang <i>et al.</i> [16]	M/65	8.5	TT	–	–	CK (+); Tg (–)
Theander <i>et al.</i> [17]	F/72	–	TT, RT, CT	T4N1M0	7	
Zimmer <i>et al.</i> [18]	F/64	–	TT, RT, CT	T4aN1M0	7	
Sarda <i>et al.</i> (6) [19]	F/50	–	PT	T4N1M0	2	
Our case <sup>b</sup>	F/48	3.2	TT, RT	T2N1M0	19 <sup>a</sup>	CK5/6, p63 (+); p53, TTF-1, Tg, calcitonin (–); Ki67 60%

<sup>a</sup>The patient was living when the article was published, <sup>b</sup>unpublished data, F – female; M – male; FNAB – fine needle aspiration biopsy; SCC – squamous cell carcinoma; ca – carcinoma; TT – total thyroidectomy; PT – partial thyroidectomy; STT – subtotal thyroidectomy; RT – radiotherapy; CT – chemotherapy

**Table 2.** Comparison of clinical and general characteristics of literature search of primary squamous cell carcinoma of thyroid gland with and without lymphocytic thyroiditis

Clinicopathological parameters	SCC with LT (n = 17)	SCC without LT (n = 77)	P-value
Gender – female	15 (23.4)	49 (76.6)	> 0.05
Age (years)	57.24 ±15.49	61.61 ±13.31	> 0.05
Tumour size (cm)	4.61 ±2.81	5.19 ±3.14	> 0.05
Lymph node metastasis	10 (62.5)	37 (53.6)	> 0.05
Extrathyroidal extension	10 (62.5)	62 (80.5)	> 0.05
Distant metastasis	0	13 (16.9)	
TNM stage			
II	3 (18.8)	2 (2.6)	< 0.05*
III	3 (18.8)	11 (14.3)	
IV A or B	10 (62.5)	51 (66.2)	
IVC	0	13 (16.9)	

Percentages are given in parentheses.

LT – lymphocytic thyroiditis; \*the p value refers to the difference between the advanced (III, IV A-B-C) and early stage (II) of primary SCC in patients with and without LT

in 18 (42.9%) patients. The second most common result of FNAB, after SCC, was poorly differentiated carcinoma (21.4%). Lymph node involvement and local invasion were found in 47 (55.3%) and 72 (77.4%) patients, respectively.

## Discussion

Primary SCC of the thyroid gland is extremely rare and aggressive. It is more common in women than in men. The median survival period of patients is usually < 1 year. Patients commonly complain of pain, swelling in the neck, hoarseness, dyspnoea, and dysphagia. Imaging techniques of the thyroid gland and neck can identify the origin and extent of the disease. Squamous cell carcinoma is the most common type of tumour in the neck and head. Therefore, it is essential to distinguish SCC from direct invasion and/or metastasis from the upper aerodigestive tract, specifically from lung and kidney tumours.

Squamous cells are not typically found in the thyroid gland. The origin of SCC in the thyroid gland is unknown. However, some hypotheses suggest that squamous cells can be derived from embryonic remnants containing squamous cells, such as the thyroglossal duct or the thymic epithelium. In addition, squamous cells can be formed through metaplasia of follicular, papillary, or anaplastic cells. This theory is supported by papillary, mixed papillary/follicular, and anaplastic carcinomas with squamous metaplasia. Another hypothesis states that squamous metaplasia of the follicular epithelium might develop due to the chronic antigenic stimulation in thyroiditis. However, if squamous metaplasia was the most common cause of SCCs, SCC would not be rare because thyroiditis is a common thyroid disease. Alternatively, primary SCC with

coexistent HT and/or LT as a pathological finding is very rare [4–19]. The literature included only four cases [4, 5, 8, 13] of primary SCC with overt HT; the longest disease (HT) duration was 3.6 years [8], compared to 16 years in our patient. Other patients had LT as the only pathological evidence.

Recent studies claimed that LT reduces the aggressiveness of papillary thyroid carcinoma (PTC) [20]. These studies also found that PTC in patients with LT was significantly associated with younger age, smaller tumour size, a lower incidence of extra-thyroidal extension, fewer distant metastases, and a lower incidence of lymph node metastasis compared with PTC in patients without LT [22]. The influence of LT on the aggressiveness or progress of primary SCC is unknown because the number of cases published is too small for a prospective study. According to our results, primary SCC in patients with LT was associated with a significantly lower incidence of distant metastasis and early disease stage at diagnosis. These results suggest that SCC with coexistent LT might be less aggressive than PTC with coexistent LT.

Lymphocytic thyroiditis is an autoimmune response to thyroid-specific antigens, which may damage the thyroid gland. Similarly, the autoimmune reaction may have a destructive effect on squamous tumour cells. Infiltrating lymphocytes in patients with primary SCC mainly derive from cytotoxic T lymphocytes, which are thought to be involved in the pathogenesis of autoimmune thyroid damage [23]. Therefore, both humoral and cytotoxic T-cell-mediated damage in chronic thyroiditis may have an effect on SCC. However, whether the presence of chronic thyroiditis affects the biological behaviour of SCCs remains uncertain.

There is no consensus concerning the treatment of primary SCC of the thyroid gland because no adequate research has been performed to date. The only treatment-related data available have been derived from case reports and small series. Generally, the recommended treatment is total thyroidectomy with lymph node dissection, followed by radiotherapy [24]. Many clinicians offer sentinel and other lymph node biopsies for suspected differentiated thyroid cancer [25] to avoid unnecessary lymph node dissection. However, the entire SCC group had a 55% chance of a lymph node metastasis diagnosis in our study. Therefore, routine lymph node dissections may be recommended for these patients. In addition, 77% of the whole group showed metastasis to surrounding tissues, which indicates that a tumour is often not completely removed and control of local and regional disease can be provided by postoperative radiotherapy with or without simultaneous chemotherapy.

Patients with primary SCC of the thyroid gland and coexisting LT were identified to have lower TNM stage and incidence of distant metastases. We hypothesised that the lymphocytic response may limit tumour growth and distant metastases in patients with SCC. To support this hypothesis, our results should be confirmed by studies with larger numbers of patients with LT and SCC.

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