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REVIEW ARTICLE

Squamous cell carcinoma of the thyroid gland: primary or secondary disease?

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Abstract

Objective: To review the aetiopathogenesis, clinical characteristics, immunohistochemical profile, prognosis and treatment options for primary thyroid squamous cell carcinoma, and to compare it with squamous cell carcinoma metastatic to the thyroid, thus providing the reader with a framework for differentiating primary and secondary disease.

Method: Review of English language literature from the past 25 years.

Search strategy: A search of the Medline, Embase and Cochrane databases (April 1984 to April 2009) was undertaken to enable a comprehensive review.

Results: After applying strict criteria for the diagnosis of primary thyroid squamous cell carcinoma, 28 articles were identified reporting 84 cases. When reviewing secondary thyroid squamous cell carcinoma, we only analysed cases of squamous cell carcinoma metastatic to the thyroid gland, and found 28 articles reporting 78 cases.

Conclusion: It is possible to differentiate between primary and secondary thyroid squamous cell carcinoma, on the basis of combined evidence from clinical examination and endoscopic, pathological and radiological evaluation. Such differentiation is important, as the prognosis for primary squamous cell carcinoma is uniformly poor irrespective of treatment, and the most suitable option may be supportive therapy. Treatment for secondary squamous cell carcinoma of the thyroid varies with the site and extent of spread of the primary tumour.

Key words: Thyroid Neoplasms; Tumour Metastasis; Squamous Carcinoma

Introduction

By definition, 'squamous cell carcinoma of [the] thyroid should be composed entirely of tumour cells with squamous differentiation'.[1] This definition gains importance when one considers that up to 43 per cent of papillary carcinomas will contain regions of squamous cell metaplasia, and that many anaplastic carcinomas will be composed, in part, of squamoid regions.[2] Additionally, adenosquamous cell carcinomas have a squamous element.

Squamous cell carcinoma (SCC) of the thyroid gland is a rare entity. It can represent either primary SCC of the thyroid gland itself or secondary involvement of the gland, due to either extension of SCC from an adjacent structure or metastasis from a distant SCC. Direct extension and metastatic involvement of the thyroid gland are more common than generally realised, occurring approximately 10 times more frequently than primary thyroid SCC.[3]

Primary SCC of the thyroid constitutes less than 1 per cent of all primary thyroid carcinomas.[4] Sporadic cases have been reported in literature, with most being derived from autopsy studies.

Advanced primary carcinomas of adjacent structures such as the tongue base, larynx, pharynx or upper oesophagus can directly invade the thyroid gland, and the gland may be the seat of metastases from SCC of the lung, head, neck or gastrointestinal tract. Despite its rich vasculature, the incidence of metastasis in the thyroid gland is low and accounts for only 2–3 per cent of all malignant tumours of the thyroid gland,[5] of which SCC forms only a small fraction.

Materials and methods

Medical literature available in English was reviewed by searching the Pubmed, Embase and Cochrane databases using the medical subject headings 'squamous

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cell carcinoma of thyroid', 'primary squamous cell carcinoma of thyroid', 'secondary squamous cell carcinoma of thyroid' and 'metastases to the thyroid', for articles published in the last 25 years (April 1984 to April 2009).

When reviewing secondary thyroid SCC, we analysed only those cases of SCC metastatic to the thyroid gland: we excluded cases of thyroid SCC which had spread from adjacent structures (e.g. tongue base, larynx, pharynx and proximal oesophagus).

The literature on metastatic involvement of the thyroid gland by SCC is difficult to analyse and compare for many reasons. We could identify no other studies specifically addressing metastasis of SCC to the thyroid gland. Most studies have analysed metastasis to the thyroid gland from a heterogeneous group of cancers. Therefore, comments from these studies regarding prognosis and management cannot be specifically applied to metastasis of SCC to the thyroid gland.

In addition, many reports are based on autopsy studies, and the unavailability of immunohistochemical analysis in earlier times makes some of the diagnoses of this era questionable.

We excluded from this review the following cases: those in which the diagnosis was based only on fine needle aspiration cytology (FNAC), without immunohistochemical analysis; those in which computed tomography (CT) scanning or autopsy were not done to exclude a primary;[6] and those in which SCC was present in association with other thyroid malignancies such as papillary carcinoma,[7,8] adenocarcinoma[6] or anaplastic carcinoma.[2]

Results

Applying the above criteria, we identified 28 case reports or case series, reporting a total of 84 cases of primary SCC of the thyroid gland occurring over the last 25 years. We analysed the treatment modalities and survival time (in months) for each of these patients, as outlined in Table I.

Table II lists the literature on metastasis to the thyroid gland published over the last 25 years (28 articles reporting 78 cases). In this table, we have attempted to separate out cases of SCC metastases to the thyroid gland, and to list their primary site(s). The lung was found to be the commonest primary site.

Discussion

Aetiopathogenesis

Primary SCC of the thyroid gland is an extremely rare neoplasm, representing less than 1 per cent of all primary thyroid malignancies.[4]

The thyroid gland does not normally contain squamous epithelium; therefore, the origin of primary SCC within the thyroid remains controversial. Several hypotheses have been proposed, but every theory has been disputed.

One of the earliest theories was proposed by Goldberg and Harvey,[63] who believed that squamous cells were derived from the embryonic remnants of the thyroglossal duct. In early embryonic life, the thyroid gland migrates downwards, and a duct may persist lined by squamous, columnar or transitional epithelium. Normally, this duct completely involutes, but if it persists it may be the source of a thyroglossal cyst or epidermoidal carcinoma. This theory has been challenged by many. The lowest part of the thyroglossal duct forms the pyramidal lobe of the thyroid gland, and if these squamous cells were to give rise to malignancy then SCC would be expected to arise in the pyramidal lobe of the thyroid gland. However, clinically, most of the reported cases of primary SCC of the thyroid originate in the lateral lobe(s).

Branchial arch remnants (e.g. the ultimobranchial body and thymic epithelium) have also been suggested as sources of squamous epithelium,[3] but these theories remain largely unproven.

A recent theory proposed that the cell of origin of pure SCC arises due to squamous metaplasia.[19] However, this appears unconvincing since the clinical conditions associated with squamous metaplasia (e.g. Hashimoto's thyroiditis) are rarely associated with primary SCC; the reviewed literature contained only three reported cases of primary SCC of the thyroid arising in association with chronic thyroiditis.[4,26,64] Secondary involvement of the thyroid gland by SCC is far more common, and can occur by direct local invasion from tumours in adjacent structures (e.g. the larynx, pharynx, proximal oesophagus, trachea, soft tissues or mediastinum), or from metastases from other sites giving rise to primary SCC (e.g. the lung, head, neck and gastrointestinal tract). Amongst SCCs of the head and neck, laryngeal and pharyngeal SCCs seem to have the greatest tendency to invade the thyroid by direct extension.[65]

Gulisano *et al.*[66] attempted to find the route of metastatic spread to the thyroid gland. In three patients with pharyngeal SCC, they injected methylene blue into the submucosa of the pyriform sinus, before commencing the surgical procedure, which included hemithyroidectomy. The superior portion of the thyroid lobe stained, from which they concluded that tumour cells tend to follow periarterial lymphatic vessels.

Clinical features

Clinically, primary thyroid SCC is very aggressive; in this respect, it resembles anaplastic thyroid carcinoma.[6] Patients typically present with a rapidly increasing neck mass invading the strap muscles, soft tissues and blood vessels of the neck, compressing the trachea and oesophagus, and having accompanying cervical lymphadenopathy. Dysphagia, dyspnoea, hoarseness and neck pain typically ensue. In contrast to primary thyroid SCC, secondary invasion of the thyroid gland from adjacent

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TABLE I
PRIMARY THYROID SCC TREATMENT AND SURVIVAL: 25-YEAR REVIEW

Study	Year	Cases (*n*)	Treatment[†]	Med survival (mth)
Long *et al.*[9]	2009	1	Surg + RT + CT	12[†]
Makay *et al.*[10]	2008	3	Surg + RT + CT	<5
Müssig *et al.*[11]	2008	1	Surg	Unknown
Fassan *et al.*[12]	2007	1	Surg	Unknown
Ab Hadi *et al.*[13]	2007	1	RT	Unknown
Chintamani *et al.*[14]	2007	3	Surg + RT	12
Booya *et al.*[15]	2006	10	Surg (8) Adj RT (10) Adj CT (4)	8.6
Sanchez-Sosa *et al.*[16]	2006	1	Surg	Unknown
Zimmer *et al.*[17]	2003	1	Surg Adj RT + CT	7
Zhou[18]	2002	4	Surg (4) Adj RT (2) Adj CT (1)	6
Sahoo *et al.*[19]	2002	2	Surg	4.5
Lam *et al.*[20]	2001	4	Surg (3) No treatment (1)	4
Agrawal *et al.*[21]	2001	1	Surg Adj RT	Unknown
Jones *et al.*[22]	2000	1	Surg	8
Cook *et al.*[23]	1999	16	Surg (2) RT (8) Surg + RT (5) RT + CT (1)	16
Kumar *et al.*[24]	1999	2	Surg (1) No treatment (1)	11
Wan Muhaizan *et al.*[25]	1998	1	Surg + RT	24[†]
Chaudhary *et al.*[26]	1994	1	Surg Adj RT	<12
Theander *et al.*[27]	1993	1	Surg Adj RT + CT	7
Tsuchiya *et al.*[28]	1990	3	Surg	5
Harada *et al.*[29]	1989	2	Surg + RT	9
Korovin *et al.*[4]	1989	4	Surg + RT + CT (3) Surg + RT (1)	8.5
Simpson & Carruthers[30]	1988	8	Surg + RT (4) Surg + RT + CT (1) Surg (1) RT + CT (2)	5
Sarda *et al.*[31]	1988	8	Surg + RT + CT	6
Misonou *et al.*[32]	1988	1	Surg Adj RT + CT	6
Riddle & Dincsoy[33]	1987	1	No treatment	3
Huang & Lin[34]	1986	1	Surg	Unknown
Kapoor *et al.*[35]	1985	1	Surg	Unknown

*Where primary treatment differed amongst a group of patients, numbers undergoing each treatment type are given in parentheses. [†]One or more patients still alive at time of writing. SCC = squamous cell carcinoma; med = median; mth = months; surg = surgery; RT = radiotherapy; CT = chemotherapy; adj = adjuvant

structures such as the larynx or tongue base is usually discovered at surgery, and confirmed by histological examination.[65] Occasionally, the presentation may be that of a neck mass, as sometimes seen in cases of proximal oesophageal SCC extending to the thyroid gland.

The clinical presentation of SCC metastases to the thyroid gland can be variable, depending largely on the extent of the primary tumour.

Lam and Lo[53] studied a series of patients with metastases to the thyroid; five of these cases were SCC, only one of which presented with an enlarging neck mass, the rest being discovered at autopsy. In contrast, Papi and colleagues'[40] case series included 11 primary thyroid SCC cases, seven of which presented clinically as a thyroid nodule.

Diagnosis

The diagnosis of thyroid SCC involves a combination of clinical examination plus endoscopic, pathological and radiological evaluation.

It is vital to exclude secondary involvement of the thyroid, from primary SCC in adjacent structures and from metastasis from the head, neck, chest, upper digestive tract and pelvis, before making a diagnosis of primary thyroid SCC.

Endoscopy

Panendoscopy should be performed to exclude a primary lesion in the nasopharynx, oropharynx, hypopharynx, larynx, oesophagus or bronchus.

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TABLE II
METASTASES TO THE THYROID GLAND: 25-YEAR REVIEW

Study	Year	Cases (*n*)	SCC cases (*n*)	Primary site(s)*	Med survival (mth)
Jankowska *et al.*[36]	2008	3	2	Tongue, tonsil	182†
Lee *et al.*[37]	2007	4	1	Lung	Unknown
Ciobanu *et al.*[38]	2007	16	7	Lung, larynx	Unknown
Iesalnieks *et al.*[39]	2007	8	–	–	–
Papi *et al.*[40]	2007	32	11	Lung, oesophagus, larynx	33
Bandyopadhyay *et al.*[41]	2006	1	1	Lung	8
Karapanagiotou *et al.*[42]	2006	1	1	Cervix	12
Cichoń *et al.*[5]	2006	17	–	–	–
Gerges *et al.*[43]	2006	7	–	–	–
Preuss *et al.*[44]	2005	1	1	Lung	12†
Mirallié *et al.*[45]	2005	29	2	Lung	26†
Kim *et al.*[46]	2005	22	6	Oesophagus, larynx, cervix	8†
Dequanter *et al.*[47]	2004	11	7	Lung, oesophagus, oropharynx	10
Wood *et al.*[48]	2004	15	1	Bladder	24
De Ridder *et al.*[49]	2003	6	1	Head & neck	14
Schwender *et al.*[50]	2002	1	1	Oral cavity	<1
Heffess *et al.*[51]	2002	36	–	–	–
Chen *et al.*[52]	1999	10	2	Lung, tongue	62†
Lam & Lo[53]	1998	79	5	Lung, cervix	Unknown
Lin *et al.*[54]	1998	14	4	Lung	3.3
Nakhjavani *et al.*[55]	1997	43	2	Lung, oesophagus	16
Rosen *et al.*[56]	1995	11	3	Oral cavity, oesophagus, lung	<24
Michelow & Leiman[57]	1995	21	4	Lung, larynx	Unknown
Smith *et al.*[58]	1987	19	3	Oesophagus, lung	9
Chaco *et al.*[59]	1987	6	–	–	–
McCabe *et al.*[60]	1985	17	11	Larynx, nasopharynx, tonsil, lung, oesophagus, cervix	12
Ivy *et al.*[61]	1984	30	2	Larynx	12
Vane *et al.*[62]	1984	8	–	–	–

*Of metastasis. †One or more patients still alive at time of writing. SCC = squamous cell carcinoma; med = median; mth = months

Radiology

There are no specific radiological features of thyroid SCC. Features similar to those seen in other thyroid malignancies are present. Ultrasound (US) is usually the first radiological modality used in the diagnostic investigation of a thyroid lump. The examination is simple and cost-effective, and is able to distinguish solid from cystic lesions and to define the echogenic pattern, which may suggest a benign or malignant tumour. Moreover, US-guided FNAC or core biopsy are also useful diagnostic modalities when combined with clinical and radiological findings.

Although CT is preferred, both CT and magnetic resonance imaging (MRI) scans are useful for the assessment of suspicious thyroid lumps. They allow differentiation of a thyroid mass from adjoining neck masses, and also enable assessment of the adjacent larynx and trachea to discern displacement, luminal narrowing, and vascular displacement and invasion. Evaluation should also assess calcification, cyst formation, necrosis, haemorrhage, lesion margin definition and extraglandular extension.[67]

Computed tomography of the chest, abdomen and pelvis helps exclude a primary source for secondary SCC of the thyroid gland.

Primary thyroid SCC often tends to encase the oesophagus rather than invade it, leaving a fat plane between the tumour and the oesophagus, which is useful in confirming that the tumour arose from the thyroid rather than the oesophagus itself.

Metastatic disease may manifest as a solitary nodular mass or, more commonly, as multiple nodular foci; in a patient with a known primary tumour, this should raise strong suspicion of metastatic disease. In addition to CT and MRI, positron emission tomography may provide useful information enabling the identification of a primary tumour in patients with occult SCC metastases to the thyroid gland.[68]

Pathology

Historical autopsy reports of primary thyroid SCC published prior to the availability of immunohistochemistry should be treated with caution. It is possible that earlier reports of primary thyroid SCC actually represent cases of secondary involvement of the thyroid from primary tumours in the trachea or oesophagus.[3]

By definition, 'squamous cell carcinoma of [the] thyroid should be composed entirely of tumour cells with squamous differentiation'.[1] However, half of primary thyroid SCC tumours are poorly differentiated. Although metastatic tumours generally retain the histological features of the primary tumour, they are frequently more poorly differentiated. The definition above should therefore be treated with caution. Primary thyroid SCC is also excluded if other types of thyroid carcinoma are present in close proximity.

A metastasis from another site should always be excluded before making a diagnosis of primary thyroid SCC.

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Fine needle aspiration cytology is of limited value, partly due to the prevalence of poorly differentiated SCC, and partly due to the inability of FNAC to reliably distinguish between primary and metastatic SCC (although it is possible that immunocytochemistry may help clarify the diagnosis).

Macroscopically, primary thyroid SCC typically involves one or both lobes of the thyroid gland, although satellite tumour nodules have been reported. In contrast, metastases to the thyroid are most often multifocal.[69]

Immunohistochemistry may be useful in distinguishing primary from metastatic thyroid SCC.

The pattern of cytokeratin expression is different in carcinomas arising from different organs, and also varies with tumour differentiation.[20] It has been reported that primary thyroid SCC is strongly positive for cytokeratin 19 but negative for cytokeratins 1, 4, 10/13 and 20.[20,70] Focal positivity for cytokeratins 7 and 18 may be present in some tumours.

Occasional cases of thyroid SCC have been reported as positive for thyroglobulin, but this probably represents non-specific absorption from adjacent cells.[24]

Thyroid transcription factor 1 expression is widely used in the diagnosis of lung and thyroid carcinomas. Thyroid transcription factor 1 is highly specific for lung and thyroid carcinoma,[71–73] and is positive in thyroid cancers regardless of histological type.[74] It is also positive in 10[74] to 30[75] per cent of lung SCC cases.

One of our own cases (not published) was thyroid transcription factor 1 positive; primary lung carcinoma was excluded by extensive clinical and radiological assessment.

Another useful marker to be considered is calcitonin, the analysis of which enables exclusion of medullary thyroid carcinoma.

Prognosis and management

Primary thyroid SCC portends a poor prognosis regardless of therapy; secondary involvement of the thyroid, however, may be more amenable to treatment.[4]

Analysis of published survival rates for the last 25 years (Table I) shows that median survival for primary thyroid SCC is poor. Ideally, survival rates for specific tumour stages should be reported, but unfortunately most case series do not mention patients' tumour stage.

Various combinations of surgery, radiotherapy and chemotherapy have been used in the treatment of primary SCC of the thyroid.

Primary thyroid SCC extensively infiltrates and invades adjacent tissue, even when small (e.g. 1–3 cm in diameter), making surgical resection extremely difficult and frequently impossible.[18]

Primary thyroid SCC has been widely reported to be relatively radio-resistant, and this conclusion is well documented in the older literature.[76–79]

Even with modern radiotherapy techniques, there has been little change in radiotherapy response rates in recent times. Sarda *et al.*[31] reported eight patients with primary thyroid SCC who were treated with post-operative chemoradiotherapy; seven out of these eight died of local recurrence within five months of surgery. In 2006, Booya *et al.*[15] reported a series of 10 cases all of which received adjuvant radiation; these patients' median survival was 8.6 months.

The relative rarity of primary thyroid SCC makes any evaluation of chemotherapy statistically inconclusive. However, the literature indicates that chemotherapy used as an adjuvant has had disappointing results. Harada *et al.*[80] reported unimpressive responses to bleomycin and to adriamycin. Shimaoka and Tsukada[78] administered nitrogen mustard, vincristine, adriamycin and AB-132 for four cases of primary thyroid SCC, but none showed any encouraging response. Similarly, other authors[6,15,23,30,31] have used chemotherapy for primary thyroid SCC but reported little benefit.

As with anaplastic thyroid carcinoma, primary thyroid SCC does not take up radioactive iodine, and thyroid-stimulating hormone suppression has little impact.[81]

Definite conclusions about the effect of chemoradiation on primary thyroid SCC cannot be drawn, due to the small number of reported cases. However, continuing modernisation in radiation techniques and advances in chemotherapy may mean that chemoradiation plays a more important role in future management of this tumour.

The cause of death in most primary thyroid SCC cases is progression of local disease, respiratory compromise, distant metastasis or treatment complications.[17,20]

Based upon our own experience of managing primary thyroid SCC patients, and upon the fact that surgery, radiation and chemotherapy in any reported combination have little or no impact in improving outcome or prolonging survival, we recommend tracheostomy (to protect the airway, as respiratory compromise is the commonest cause of death in these patients), PEG (Percutaneous endoscopic gastrostomy) or open gastrostomy (as dysphagia from oesophageal invasion is common), and supportive treatment, rather than radical chemoradiation and surgery. The latter are by no means curative, and there is little evidence to show that they prolong life. However, there remains a limited but important role for palliative surgery, in the form of total thyroidectomy to relieve severe airway obstruction.

The management of SCC metastasis to the thyroid is poorly documented in the literature, primarily because the majority of reports are derived from pathology journals that do not comment on patient management or prognosis. In addition, the site of primary disease is so variable (including tongue, tonsil, larynx, oesophagus, cervix and bladder) that general comments about treatment cannot be made. Management depends on the site and stage of the primary tumour, the presence of other metastases, and the symptoms caused by the thyroid metastases.

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We recommend that patients with treatable primary SCC should undergo total thyroidectomy for isolated metastases to the thyroid gland, not only to prolong survival but also to prevent further dissemination of the tumour (taking into account the rich blood supply of the thyroid gland, which would favour leakage of tumour emboli into the systemic circulation).[82]

Conclusion

Squamous cell carcinoma of the thyroid gland is an uncommon condition and represents a diagnostic dilemma both for the otolaryngologist, who needs a thorough evaluation, and the pathologist. It is vital to differentiate primary and secondary involvement of the thyroid gland by SCC, as the prognosis and management of the two conditions can differ significantly.[82]

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