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Review

Metastasis of squamous cell carcinoma of the head and neck to the thyroid: a single institution's experience with a review of relevant publications

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Abstract

The thyroid gland is a rare site of metastasis, and in particular of those of squamous cell carcinoma (SCC) from the head and neck region. We have reviewed the aetiology, pathogenesis, clinical characteristics, radiological features, immunohistochemical profile, prognosis, and management of metastatic SCC from the head and neck region to the thyroid, and searched current publications on the Medline, Embase, and Cochrane databases using the following keywords: "SCC of thyroid", "secondary SCC of thyroid", and "metastasis to the thyroid", for papers published during the last 33 years (April 1984 to October 2017).We found a total of 19 papers that reported a total of 32 cases that were relevant. Four further cases were discovered as an incidental finding on follow-up positron emission tomographic/computed tomographic scans with magnetic resonance imaging of the head and neck at our hospital, which were confirmed with an ultrasound-guided core needle biopsy followed by immunohistochemical examination. For patients who are doing well, whose disease is controlled at the primary site, and who have no evidence of distant metastatic disease, total thyroidectomy could be considered followed by adjuvant radiation or chemoradiotherapy, depending on the presence of intermediate or high-risk features on pathological examination and previous history of radiation. This may help to control the disease and avoid local morbidity.

Keywords: secondary squamous cell carcinoma of thyroid; metastasis to thyroid; head and neck squamous cell carcinoma metastasis

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Introduction

Metastasis to the thyroid gland is not common in clinical practice. An overall incidence of secondary thyroid malignant tumours ranging from 1.2% to 24% has been reported in necropsy series.[1–3] In surgical series the incidence is even lower, between 0.6% and 2.2%.[4,5] The reason for the difference between clinical and necropsy studies can be explained by the evidence of clinically occult micrometastases in most cases.[3]

Squamous cell carcinoma (SCC) of the thyroid gland is rare, and can present itself as either primary SCC of the thyroid gland or secondary involvement of the gland itself as a result of either extension of an SCC from an adjacent structure or a metastasis from a distant SCC. Direct extension and metastatic involvement are more common, and occur about 10 times more frequently than primary thyroid SCC, which makes up less than 1% of all primary thyroid carcinomas.[6,7]

Despite it having a rich vasculature the incidence of metastases to the thyroid gland is low and accounts for only 2%–3% of all malignant tumours of the thyroid, of which SCC forms a small fraction.[8]

Patients, material, and methods

We searched the Medline, Embase, and Cochrane databases using the keywords "SCC of thyroid", "secondary SCC of thyroid", and "metastasis to the thyroid", for papers published on the subject during the last 33 years (April 1984 - October 2017).

Inclusion criteria

Only cases of SCC of the head and neck that had metastasised to the thyroid were included.

Exclusion criteria

We excluded cases of SCC of the thyroid that had spread by direct extension from adjacent structures, those in which the diagnosis was based only on fine needle aspiration cytology without immunohistochemical analysis, those in which computed tomographic (CT) scanning or necropsy were not done to exclude the primary, and those where the SCC was coexisting with any other thyroid malignancies (such as papillary carcinoma, adenocarcinoma, or anaplastic carcinoma).

Results

After a thorough review of the available data we realised that there were few if any comprehensive studies of SCC that had metastasised from the head and neck to the thyroid. This also made the data difficult to analyse, as most studies had reported metastasis to the thyroid gland from a heterogeneous group of cancers as well from different subsites throughout the entire body.

We found a total of 19 papers that reported a total of 32 patients with SCC of the head and neck that had metastasised to the thyroid gland (Table 1). In addition a total of four were diagnosed at our centre (Supplemental data, online only, Table 2.), three of whom had primary disease in the oral

Table 1
Review of published reports.

First author, year, and reference	Site of primary	Median survival (months)	No. with SCC
Ivy 1984[9]	Larynx	12	1
McCabe 1985[10]	Larynx, nasopharynx, tonsil	12	7*
Jalaludin 1994[11]	Nasopharynx	Unknown	1
Michelow 1995[12]	Larynx	Unknown	1
Amin 1995[13]	Nasopharynx	Unknown	1
Rosen 1995[14]	Oral cavity	<24	1
Chen 1995[15]	Tongue	62†	1
Schwender 2002[16]	Oral cavity	<1	1
De Ridder 2003[17]	Head and neck	14	1
Dequanter 2004[18]	Oropharynx	10	1
Kim 2005[19]	Larynx	8†	1
Papi 2007[20]	Larynx	33	4
Ciobanu 2007[21]	Larynx	Unknown	2
Jankowska 2008[22]	Tongue, tonsil, nasopharynx	182†	3
H 2009[23]	Nasopharynx	Unknown	1
Chiumento 2011[24]	Nasopharynx	11†	1
Osmany 2011[25]	Nasopharynx	Unknown	1
Aparici 2017[26]	Tonsil, larynx	Unknown	2
Lewis 2017[27]	Nasopharynx	8†	1

† One or more patients still alive at time of writing, SCC = squamous cell carcinoma.

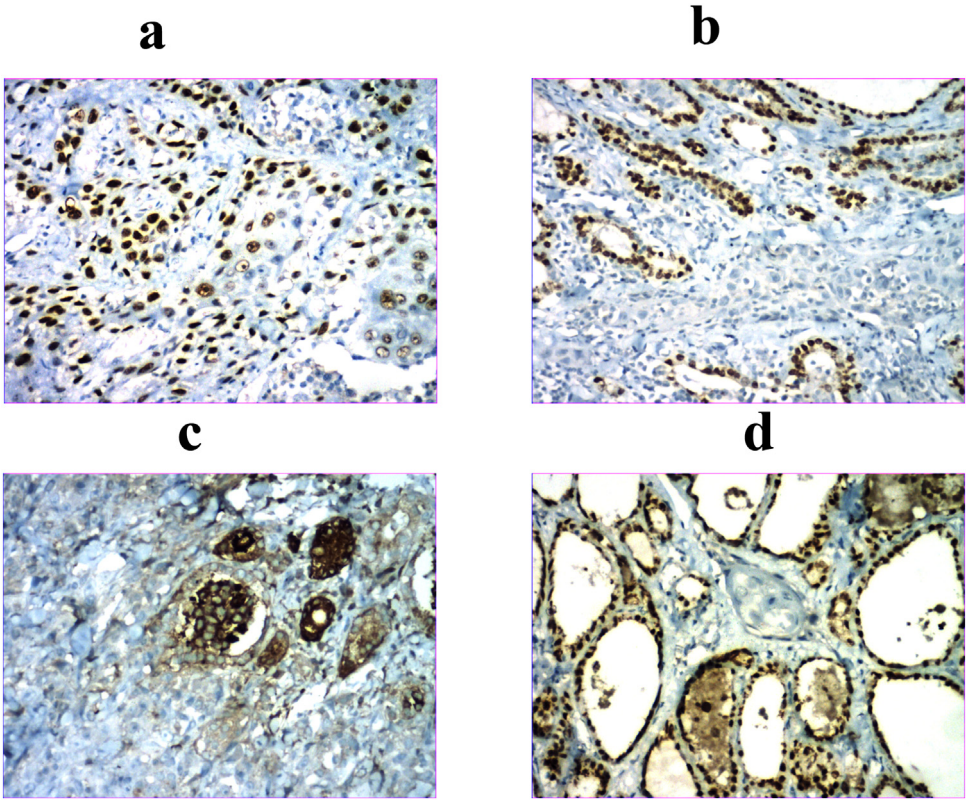

Fig. 1. (a) Squamous cell carcinoma metastatic cells to the thyroid gland showing a pattern of good immunoreactivity for p63 (IHC, x 400). (b) Thyroid transcription factor-1 (TTF1) shows negative pattern of immunoreactivity in squamous cell carcinoma metastatic cells to thyroid gland. Normal thyroid follicles show good immunoreactivity (IHC, x 100). (c) Thyroglobulin shows negative pattern of immunoreactivity in SCC metastatic cells to thyroid gland. Normal thyroid follicles show good immunoreactivity (IHC, x 100). (d) PAX8 shows negative immunoreactivity in SCC metastatic cells to thyroid gland. Normal thyroid follicles show good immunoreactivity (IHC, x 100).

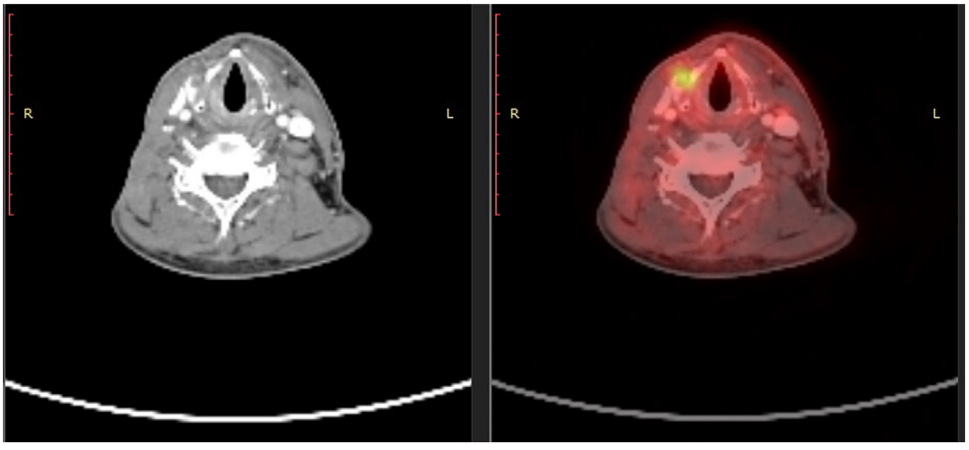

Fig. 2. (Case 1): Positron emission tomographic/computed tomographic image showing few hypodense ill-defined lesions in the right lobe and isthmus, extending into the left lobe of thyroid. The largest nodule measured 30 x 23 mm in the isthmus on the left side with foci of calcification within. The right lobe nodule measured 16 x 15 mm.

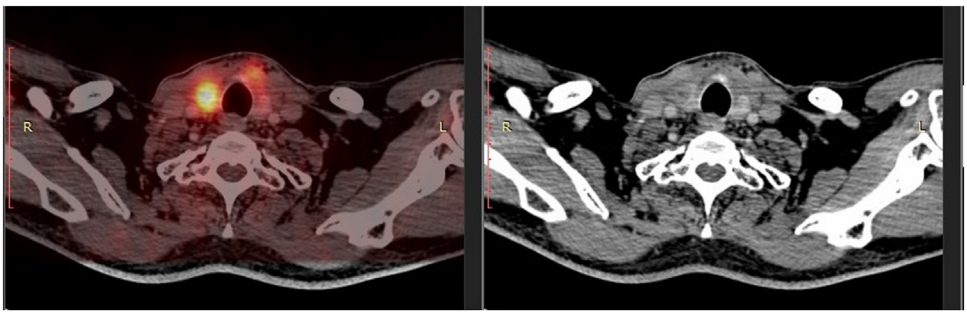

Fig. 3. (Case 4): Positron emission tomographic/computed tomographic image showing high grade FDG heterogeneously enhancing the lesion in the enlarged right lobe and right part of isthmus of the thyroid gland. The lesion measured 14 × 10 x 20 mm.

cavity and one in the larynx. Metastasis to the thyroid gland was confirmed with ultrasound-guided core needle biopsy and immunohistochemistry, and the histopathological findings were similar for both the primary site and the metastatic lesion. Immunohistochemistry showed cytokeratin 5/6 (++), tumour protein 63 (++), thyroid transcription factor-1 (-), thyroglobulin (-), and PAX 8 (-) (Fig. 1a–d).

Metastasis to the thyroid showed as incidental findings on follow-up positron emission tomography (PET) CT with magnetic resonance fusion, which showed increased uptake of fluorodeoxyglucose (FDG) at the metastatic site in the thyroid (Fig. 2). Total thyroidectomy was done for two patients and hemithyroidectomy for one. The remaining one patient had no treatment and died four months after the thyroid metastasis was diagnosed. The overall survival was 6 months and 27 months after total thyroidectomy and 4 months after hemithyroidectomy. The latter patient had residual disease in the thyroid postoperatively and was given palliative treatment. The other 3 patients died of distant metastases to the lungs (Fig. 3).

Discussion

Aetiology and pathogenesis

Secondary involvement of the thyroid gland by SCC can occur by direct local invasion from tumours in adjacent structures (such as the larynx, pharynx, proximal oesophagus, trachea, soft tissues or mediastinum), or from metastasis from a primary site. Among SCC of the head and neck, the greatest trend in the involvement of the thyroid was direct extension from the SCC in the larynx and pharynx.[28]

Observational data have shown that metastasis seems to be more likely in thyroid glands that are already abnormal. It has been hypothesised that this may be a result of the slowing of intraparenchymal blood flow in nodular thyroid glands (such as multinodular goitre, or solitary thyroid nodule).[2,12]

Diagnosis

The diagnosis of metastatic SCC to the thyroid is usually incidental during investigations of the primary SCC in the head and neck, and involves a combination of clinical examination, and pathological and radiological evaluation.

Clinical features

The clinical presentation of metastasis of SCC to the thyroid can vary. There may be no mass or nodule palpable clinically in the neck, but the occasional presentation of a small nodule. Symptoms of dysphagia, dyspnoea, stridor, hoarseness, and neck pain (although rare) may be found in slightly aggressive disease, and in such cases it is important to differentiate it from a primary thyroid SCC. The mobility of the vocal cord should be noted preoperatively.

Lam and Lo studied a series of patients with metastasis to the thyroid, 5 of whom had SCC. However, only one of them presented with an enlarging neck mass, the rest being discovered at necropsy.[2] In all 4 of the cases who presented to us, no mass was palpable clinically and nor did the patients have any symptoms. Metastasis to the thyroid was discovered as incidental findings during follow up PET – CT scans.

Radiological findings

No specific radiological features were seen in cases of metastasis of SCC to the thyroid, but the features are similar to those seen in any other malignancy. Ultrasound is usually the first radiological diagnostic investigation. The examination is simple, cost-effective, and can distinguish solid from cystic lesions. It defines the echogenic pattern, which may suggest a benign or malignant tumour. It should always be followed by an ultrasound-guided core needle biopsy.

Although CT is preferred, both CT and magnetic resonance imaging (MRI) scans are useful for the assessment of suspicious thyroid nodules. They allow differentiation of a thyroid mass from adjoining neck masses, and enable assessment of the adjacent larynx and trachea to discern displacement, luminal narrowing, and vascular displacement and invasion. Evaluation should also assess calcification, cystic formation, necrosis, haemorrhage, and definition of the margins of a lesion and its extra glandular extension.[29]

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

Metastatic disease may show itself as a solitary nodular mass, or as multiple nodular foci; in a patient with a known primary tumour this raises a strong suspicion of metastatic disease. In addition to CT and MRI, PET may provide useful information that enables the identification of any metastasis to the thyroid gland in case of a known primary SCC of the head and neck. At our hospital we usually prefer PET CT combined with magnetic resonance fusion as it helps to identify even a small, solitary, metastatic nodule in the thyroid gland. A focal thyroid lesion with appreciable uptake is likely to be malignant, whereas diffuse increased uptake favours several thyroidal disorders that include chronic thyroiditis, Graves disease, diffuse goitre, and multinodular goitre.[30] The risk of malignancy is as high as 63.6% in thyroid lesions with focal uptake.[31]

Histopathology

Fine needle aspiration cytology is of limited value, partly because of the prevalence of poorly differentiated SCC, and partly because of the inability of fine-needle aspiration cytology to distinguish reliably between primary and metastatic SCC. An ultrasound-guided core needle biopsy yields a good amount of tissue for diagnostic purposes.

Macroscopically, primary thyroid SCC typically involves one or both lobes of the gland,although satellite nodules of tumour have been reported. In contrast, metastasis to the thyroid is usually multifocal.[32]

Immunohistochemistry alone is largely unhelpful in definitively distinguishing primary from metastatic thyroid SCC but should be used as an additional diagnostic tool. The pattern of cytokeratin expression is different in carcinomas that arise from different organs, and varies with differentiation of the tumour.[33] Immunostaining for both p63 and CK5/6, particularly in poorly differentiated metastatic carcinomas, is highly predictive of a primary tumour of squamous epithelial origin.[34]

Thyroglobulin positivity is seen in primary thyroid lesions.[35,36] Thyroid transcription factor 1 is highly specific for lung carcinomas and a large percentage (>95%) of follicular, papillary, and insular thyroid carcinomas express it.[37–40]

PAX8 immunostaining is a reliable way of discerning the thyroid origin of undifferentiated tumours such as anaplastic thyroid carcinoma.[41] It has also been reported to be positive in primary thyroid SCC, and is rarely expressed in SCC of the lungs, larynx, thymus, or the skin. PAX8 staining is therefore useful in distinguishing primary thyroid SCC from invasion or metastasis from extrathyroidal SCC.[42,43]

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

Prognosis and management

The management of metastasis of SCC to the thyroid is a grey area, primarily because most reports are derived from pathology journals that do not comment on management of the patient or prognosis of the condition. The site of primary disease in published cases also varies, which makes it difficult to derive a single management protocol. Management depends on the site and stage of the primary tumour, the presence of other metastases, and the symptoms caused by the thyroid metastases.

Several reports have documented the poor outcome for patients with intrathyroid metastasis; however, an overall review of the evidence suggests that thyroidectomy may be beneficial, even if it is a palliative procedure to reduce the incidence of locally recurrent tumour and can be associated with long-term survival.[4,5,15]

In our experience, in patients who respond well, whose disease is controlled at the primary site, and who have no evidence of distant metastatic disease, radical treatment should be considered. This may possibly prolong survival and prevent further dissemination of the tumour by the systemic circulation by the rich vascular supply of the thyroid (Leeman JE, et al. Long-term survival in oligometastatic head and neck cancer. Paper presented at the 59th meeting of the American Society of Radiation Oncology, San Diego, 2017). Surgery, which is often the initial treatment of choice, may be challenging.

Of the 4 cases reported from our centre, 3e were operated on - 2 had total thyroidectomy and one hemithyroidectomy. The latter patient had residual disease at the operation site in the thyroid and metastasis in the contralateral lobe one month postoperatively.

Because most cases of metastasis to the thyroid gland have been given radiotherapy to the neck they have severe fibrosis, with the thyroid gland adherent to the surrounding structures such as the trachea, recurrent laryngeal nerve, strap muscle, and oesophagus, and separation of the thyroid from these structures is technically difficult. An adequate resection is generally defined as tumour-free margins of soft tissue, and an inability to achieve this leads to local recurrence in the near future. This is extremely difficult to manage and is distressing for the patient. The parathyroid glands are difficult to identify as well as being separate from the thyroid. All attempts should be made to preserve the recurrent laryngeal nerve on at least one side, in case it is difficult to separate the thyroid from the nerve to decrease the morbidity.

Adjuvant radiation or chemoradiotherapy may be offered to the patient, depending on the presence of intermediate-risk or high-risk features histologically. Further full-dose irradiation of a small volume (with no elective nodal reirradiation) postoperatively, and in combination with chemotherapy, may offer potential for long-term survival. In patients for whom this means further irradiation, the latent period since the previous treatment should be over 6 months, with no obvious evidence of late radiation damage.[37]

Radiation and chemotherapy alone may offer some palliative benefit, but for the most part, are thought to be unsatisfactory. In the context of disseminated metastatic disease, management depends on the current health of the patient, coexisting conditions, estimated life expectancy, and

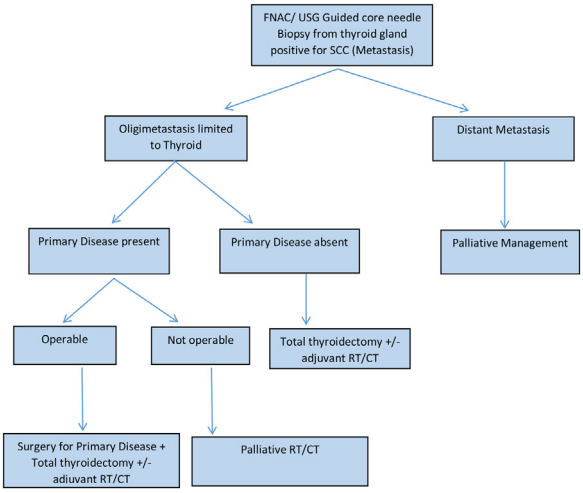

Fig. 4. Algorithm for management of metastasis of squamous cell carcinoma of the head and neck to thyroid.

the patient's wishes. Palliative chemotherapy should be considered in addition to best supportive care, although surgery can also be considered for relief or prevention of local symptoms.

Conclusion

Isolated metastasis to the thyroid gland from SCC of the head and neck is rare. In patients with reasonable health, control of disease at the primary site, and no evidence of distant metastatic disease, radical treatment could be considered. Resection in the form of total thyroidectomy may be followed by adjuvant radiation or chemoradiotherapy, depending on the presence of intermediate-risk or high-risk features on histopathological examination and previous radiation history. The treatment algorithm (Fig. 4) we have presented is based on our limited experience of four cases and can be considered to control the local recurrence of the tumour and its related morbidity, and possibly aid the long-term survival of the patient.

Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patients' permission

Ethics approval not required. The patients' permission for publication was obtained.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.bjoms.2019.05.012.

References

1. Mortensen JD, Woolner LB, Bennett WA. Secondary malignant tumors of the thyroid gland. *Cancer* 1956;**9**:306–9.
2. Lam KY, Lo CY. Metastatic tumors of the thyroid gland: a study of 79 cases in Chinese patients. *Arch Pathol Lab Med* 1998;**122**:37–41.
3. Shimaoka K, Sokal JE, Pickren JW. Metastatic neoplasms in the thyroid gland: pathological and clinical findings. *Cancer* 1962;**15**: 557–65.
4. Menegaux F, Chigot JP. Thyroid metastases. *Ann Chir* 2001;**126**:981–4 (in French).
5. Pitale SU, Sizemore GW, Bakhos R, et al. Renal cell carcinoma with metastasis to the thyroid gland. *Urol Oncol* 2000;**5**:173–5.
6. Goldman RL. Primary squamous cell carcinoma of the thyroid gland. Report of a case and review of literature. *Am Surg* 1964;**30**:247–52.
7. Korovin GS, Kuriloff DB, Cho HT, et al. Squamous cell carcinoma of the thyroid: a diagnostic dilemma. *Ann Otol Rhinol Laryngol* 1989;**98**:59–65.
8. Cichon S, Anielski R, Konturek A, et al. Metastases to the thyroid gland: seventeen cases operated on in a single clinical center. *Langenbecks Arch Surg* 2006;**391**:581–7.
9. Ivy HK. Cancer metastatic to the thyroid: a diagnostic problem. *Mayo Clin Proc* 1984;**59**:856–9.
10. McCabe DP, Farrar WB, Petkov TM, et al. Clinical and pathologic correlations in disease metastatic to the thyroid gland. *Am J Surg* 1985;**150**:519–23.
11. Jalaludin MA, Rajadurai P, Va R, et al. Thyroid metastasis from nasopharyngeal carcinoma: a case report. *J Laryngol Otol* 1994;**108**:886–8.
12. Michelow PM, Leiman G. Metastases to the thyroid gland: diagnosis by aspiration cytology. *Diagn Cytopathol* 1995;**13**:209–13.
13. Amin R. Thyroid metastasis from nasopharyngeal carcinoma: a case report. *J Laryngol Otol* 1995;**109**:1130.
14. Rosen IB, Walfish PG, Bain J, et al. Secondary malignancy of the thyroid gland and its management. *Ann Surg Oncol* 1995;**2**:252–6.
15. Chen H, Nicol TL, Udelsman R. Clinically significant, isolated metastatic disease to the thyroid gland. *World J Surg* 1999;**23**:177–781.
16. Schwender FT, Wollner I, Kunju LP, et al. Squamous cell carcinoma of the buccal mucosa with metastases to the pericardial cavity, lung and thyroid. *Oral Oncol* 2002;**38**:114–6.
17. De Ridder M, Sermeus AB, Urbain D, et al. Metastases to the thyroid gland – a report of six cases. *Eur J Intern Med* 2003;**14**:377–9.
18. Dequanter D, Lothaire P, Larsimont D, et al. Intrathyroid metastasis: 11 cases. *Ann Endocrinol (Paris)* 2004;**65**:205–8 (in French).
19. Kim TY, Kim WB, Gong G, et al. Metastasis to the thyroid diagnosed by fine-needle aspiration biopsy. *Clin Endocrinol (Oxf)* 2005;**62**: 236–41.
20. Papi G, Fadda G, Corsello SM, et al. Metastases to the thyroid gland: prevalence, clinicopathological aspects and prognosis: a 10-year experience. *Clin Endocrinol (Oxf)* 2007;**66**:565–71.
21. Ciobanu D, Vulpoi C, Galusca B, et al. The value of the immunohistochemical exam in the diagnosis of the secondary malignant tumors to the thyroid gland. *Rom J Morphol Embryol* 2007;**48**:113–9.
22. Jankowska P, Teoh EM, Fisher C, et al. Case report. Isolated intrathyroid metastasis from undifferentiated and squamous carcinoma of the head and neck: the case for surgery and re-irradiation. *Br J Radiol* 2008;**81**:154–61.
23. Dhouib H, Ben Hmida A, Daoud J, et al. A case of thyroid metastasis of an unusual cancer. *Cancer Radiother* 2009;**13**:213–5.
24. Chiumento C, Fiorentino A, Castaldo G, et al. A case of thyroid metastasis of nasopharyngeal cancer. *Tumori* 2011;**97**:24e–6e.

25. Osmany S, Padhy AK, Ng DC. Detection of thyroid metastases from nasopharyngeal carcinoma with F-18 FDG PET/CT. *Clin Nucl Med* 2008;**33**:224–5.
26. Aparici CM, Win AZ. Two cases of thyroid metastasis from head and neck squamous cell carcinoma detected by FDG-PET/CT. *J Clin Imaging Sci* 2014;**4**:62.
27. Lewis SC, D'cruz AK, Joshi A, et al. Thyroid mass: Metastasis from nasopharyngeal cancer – an unusual presentation. *Indian J Palliat Care* 2017;**23**:104–8.
28. Nakhjavani M, Gharib H, Goellner JR, et al. Direct extension of malignant lesions to the thyroid gland from adjacent organs: report of 17 cases. *Endocr Pract* 1999;**5**:69–71.
29. Tateishi U, Gamez C, Dawood S, et al. Chronic thyroiditis in patients with advanced breast carcinoma: Metabolic and morphologic changes on PET-CT. *Eur J Nucl Med Mol Imaging* 2009;**36**:894–902.
30. Chen W, Parsons M, Torigian DA, Zhuang H, Alavi A. Evaluation of thyroid FDG uptake incidentally identified on FDG-PET/CT imaging. *Nucl Med Commun* 2009;**30**:240–4.
31. DeLellis R, et al. Secondary tumours of the thyroid. In: DeLellis R, Lloyd RV, Heitz PU, editors. *Pathology and genetics of tumours of endocrine organs. WHO Classification of tumours*, Vol. 8, 3rd ed Lyon: IARC Press; 2004. p. 122–3.
32. Lam KY, Lo CY, Liu MC. Primary squamous cell carcinoma of the thyroid gland: an entity with aggressive clinical behaviour and distinctive cytokeratin expression profiles. *Histopathology* 2001;**39**:279–86.
33. Lam KY, Lui MC, Lo CY. Cytokeratin expression profiles in thyroid carcinomas. *Eur J Surg Oncol* 2001;**27**:631–5.
34. Kaufmann O, Fietze E, Mengs J, et al. Value of p63 and cytokeratin 5/6 as immunohistochemical markers for the differential diagnosis of poorly differentiated and undifferentiated carcinomas. *Am J Clin Pathol* 2001;**116**:823–30.
35. Ordóñez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;**24**:1217–23.
36. Wagner K, Arciaga R, Siperstein A, et al. Thyrotropin receptor/thyroglobulin messenger ribonucleic acid in peripheral blood and fine-needle aspiration cytology: diagnostic synergy for detecting thyroid cancer. *J Clin Endocrinol Metab* 2005;**90**:1921–4.
37. Pelosi G, Fraggetta F, Pasini F, et al. Immunoreactivity for thyroid transcription factor-1 in stage I non-small cell carcinomas of the lung. *Am J Surg Pathol* 2001;**25**:363–72.
38. Dabbs DJ. Immunohistology of endocrine tumours. In: Dabbs DJ, editor. *Diagnostic immunohistochemistry*. 2nd ed Philadelphia: Churchill Livingstone; 2006. p. 269.
39. Salama JK, Vokes EE, Chmura SJ, et al. Long-term outcome of concurrent chemotherapy and reirradiation for recurrent and second primary head-and-neck squamous cell carcinoma. *Int J Radiat Oncol Biol Phys* 2006;**64**:382–91.
40. Treadwell T, Alexander BB, Owen M, et al. Clear cell renal carcinoma masquerading as a thyroid nodule. *South Med J* 1981;**74**:878–9.
41. Bishop JA, Sharma R, Westra WH. PAX8 immunostaining of anaplastic thyroid carcinoma: a reliable means of discerning thyroid origin for undifferentiated tumors of the head and neck. *Hum Pathol* 2011;**42**:1873–7.
42. Suzuki A, Hirokawa M, Takada N, et al. Diagnostic significance of PAX8 in thyroid squamous cell carcinoma. *Endocr J* 2015;**62**:991–5.
43. Ozcan A, Shen SS, Hamilton C, et al. PAX 8 expression in non-neoplastic tissues, primary tumors, and metastatic tumors: a comprehensive immunohistochemical study. *Mod Pathol* 2011;**24**:751–64.