Papillary microcarcinoma of the thyroid: a review

R.M.T.M Gunawardena, L.A Ranasinghe
National Hospital of Sri Lanka

Abstract

Papillary cancers of the thyroid less than 1cm in diameter are defined as microcarcinomas. Although considered as a disease with an indolent course with excellent long term prognosis a significant proportion with this condition will have lymph node metastasis at diagnosis. Clinicians need to be aware of the pathological characteristics, natural history and the internationally accepted treatment strategies when managing patients with micropapillary cancers as increasing numbers of patients are expected to be diagnosed with this condition due to widespread use of imaging modalities for numerous other indications. This brief review aims to summarize these aspects with emphasis on management.

Introduction

Microcarcinoma of the thyroid is defined as a tumor less than 1cm in its maximum diameter [1]. Mostly they are of the papillary variety although rarely they can be of follicular or medullary in type [2]. Although epidemiological data regarding the prevalence of thyroid cancer in Sri Lanka is not readily available, international studies report a rising incidence of thyroid cancers over the past few decades. Increased diagnosis of small papillary cancers accounts for the overwhelming majority of this rise [3]. Despite this increase in the disease burden, management of this entity is controversial [3] with some advocating aggressive treatment and others a more conservative approach.

Clinical presentation

The mean age of diagnosis of thyroid microcarcinoma ranges from 41.9–55 years and there is a female preponderance. Clustering of papillary microcarcinomas (microPTCs) among family members have also been reported [4].

Most of the papillary microPTCs are usually not palpable and they are detected incidentally on thyroidectomy specimens performed for other indications [5]. The detection rate of such 'incidental' microPTC ranges from 2.2 - 49.9% in thyroid glands removed for benign causes and depends on the thoroughness of histopathological examination [2].

Asymptomatic, unsuspected thyroid lesions found on imaging studies or surgeries unrelated to the thyroid are defined as 'thyroid incidentalomas' [6]. Increased detection of such lesions mainly due to liberal use of ultra sound scanning has contributed to the rising incidence of thyroid cancer [3]. Nodules are detected on 13-67% of thyroid glands on ultrasound [4]. As they are common findings, to guide clinicians as to when to perform guided fine needle aspiration cytology (FNAC), ultrasonically suspicious features for malignancy have been described such as microcalcifications, increased vascularity in the centre of the tumor compared to surrounding normal thyroid tissue, hypoechogenicity, irregular borders and taller than wider dimensions of the nodule [5,7]. Some thyroid incidentalomas may prove to be malignant upon FNAC.

Autopsy studies have reported 'latent' microPTC in 5.6 - 28.4 % (8) of the analyzed specimens.

The entity of 'occult' microPTC includes lesions detected upon search for the origin of lymph node or visceral metastasis [10].

Pathologic characteristics

Pathologically, microPTCs do not exhibit different morphological characteristics compared to classical papillary carcinomas [11]. They are likely to be located near the capsule of the thyroid gland and are non-encapsulated. Histologically, characteristic orphan Annie eyed nuclei are seen. Variants of classical papillary carcinoma such as follicular, tall cell and oncocytic types may also be seen in the microcarcinoma counterpart [4].

Characteristically, microPTCs are slow growing [10]. A Japanese study reported that only 6.4% and 15.9% of followed up microPTCs showed an increase in the size > 3mms at 5 years and 10 years, respectively [12]. However, in contrast a significant proportion of these tumors may be multifocal or bilateral. In surgical specimens, multifocality ranged from 15% - 43.8% [9]. So et al. reported bilateral

Correspondence: Thilina Gunawardena
E-mail: mihirangn@gmail.com
Received: 06-03-2017 Accepted: 29-03-2017
http://orcid.org/0000-0002-3867-2780
DOI: http://doi.org/10.4038/sljs.v35i2.8383

tumours in 63 of 277 (22.7%) patients with microPTC. They identified that nodular hyperplasia of the gland was a risk factor for both multifocal and bilateral tumors. The same authors reported that the presence of multifocal lesions in a single lobe was associated with a higher chance of bilateral tumours [13].

Lymph node metastasis are present in up to 64% of the patients at the time of diagnosis of microPTC [4]. Wada et al who did prophylactic central compartment lymphadenectomy in clinically node negative patients with microPTC who underwent thyroidectomy, reported that up to 60.9% had involved nodes [14]. Larger primary lesions, follicular variant of microPTC and the extension of the lesion beyond the thyroid capsule are identified as risk factors for lymph node metastasis [4].

Although it is a rare possibility, metastatic deposits in organs other than lymph nodes can be present at the diagnosis of microPTC. In the meta analysis published by Roti et al, they noted that out of 9313 patients with microPTC only 35 (0.37%) had such a presentation. The authors noted that larger primary tumors, presence of lymph node metastasis, follicular variant and increasing age as risk factors for distant metastasis at diagnosis [4].

Comparison of clinically overt microPTC versus incidentally detected microPTC have shown that, adverse features such as the presence of multifocality/bilaterality, extension beyond the thyroid capsule, presence of lymph node or extra lymph node metastasis were higher in the former group [4].

Genetics- BRAF mutation

Mutations in the BRAF proto oncogene is considered the most common genetic alteration in papillary thyroid cancers [25]. It is detected in up to 83% of all papillary thyroid cancers and 30% of microPTCs [25, 26]. Detection of this mutation may have a role in diagnosis, prognosis and development of management strategies for papillary cancers of the thyroid. Studies have reported a higher incidence of adverse features such as involvement of perithyroidal tissues and nodal metastasis in BRAF mutation associated microPTCs [26]. As there is a lack of specific clinicopathologic indicators to determine which microPTCs need aggressive treatment, detection of BRAF mutation may play a role in solving this dilemma [25].

Management

MicroPTC is considered as a disease with a good prognosis and the mortality is considered to be less than 1% [2]. In their meta-analysis, Roti et al. reported a disease specific death rate of 0.34% (32/9379) [4]. However, some authors describe two biologically distinct subtypes of microPTC, one type with an indolent behavior with minimal or no disease progression, the other type being more aggressive with potential for dissemination [15]. However the authors agree that clearly defined criteria to determine which type is which are still lacking.

The local recurrence rates after resection of primary microPTCs ranges from 3.8-20%, and cervical lymph nodes are the preferred site of recurrence[2]. Patient age (<45 years), clinically overt disease, lymph node metastasis at diagnosis, cancer multifocality [4], poorly differentiated cancers, presence of a desmoplastic reaction and/or invasion of perithyroidal tissue [2] have been identified as risk factors for recurrent disease. Male gender, primary tumour size and presence of tumor extension beyond the thyroid capsule have been recognized by some as predictors of local recurrence but not by others [2, 4, 16].

The long term survival is virtually 100% in microPTC without clinical evidence of nodal or distal metastasis at diagnosis, hence the aim of treatment should be to achieve disease control without undue treatment associated morbidity [2].

For unifocal microPTC with no extension beyond the thyroid capsule, lymph node or distant metastasis resection of the affected lobe is the recommended treatment [2]. National Comprehensive Cancer Network (NCCN) guidelines recommends consideration of total thyroidectomy if there are additional risk factors such as a history of irradiation of the neck, poorly differentiated tumors, or bilateral nodularity of the gland [17].

If a microPTC is detected in a lobectomy specimen performed for another indication, staging of the neck by ultrasound should be considered. Completion thyroidectomy is indicated for FNAC proven contralateral lesions or lymph node metastasis [17].

Follow up of patients who have undergone lobectomy is by physical examination, serum TSH, thyroglobulin and anti-thyroid antibodies at 6 and 12 months after surgery and annually thereafter if there is no evidence of recurrent or residual disease as recommended by NCCN guidelines [17]. However, it has been argued that patients with microPTC without risk factors on whom lobectomy has been performed have no additional risk of dying from thyroid cancer compared to the general population. Hence British guidelines for the management of thyroid cancer advocates no further follow-up regarding cancer care in such patients [2].

Total thyroidectomy is the standard treatment for microPTC with lymph node metastasis, distant metastasis, or local invasion [17]. According to British guidelines for the management of thyroid cancer, total thyroidectomy is also indicated for patients with microPTC and familial non medullary thyroid cancer [4].

For patients with multifocal microPTC total thyroidectomy should be offered [2]. According to literature lobectomy/and or isthmathectomy for multifocal disease leads to higher recurrence rates (8.2-25%) compared to total thyroidectomy done for the same indication (2.3-5%) [17].

Therapeutic neck dissection combined with total thyroidectomy should be performed for microPTC presenting with lymph node metastasis [2]. Lymph node involvement at diagnosis has a 11- 22% risk of future recurrence in lymph nodes [18]. It is also associated with higher risk of distant metastasis [4, 19].

According to British guidelines prophylactic central compartment neck dissection(PCCND) in microPTC can be considered for multi focal disease, presence of perithyroidal tissue invasion and extra thyroidal disease [2]. However, PCCND in node negative papillary thyroid carcinoma does not offer a survival benefit nor does it significantly reduce local recurrence rates [20]. Regarding the morbidity of prophylactic neck dissection Caliskan et al. reported permanent hypoparathyroidism and recurrent laryngeal nerve palsy at a rate of 2.6%. And 0.5% after performing the procedure on 842 patients with micoPTC [21].

MicoPTC presenting with extra nodal metastasis is extremely rare, and it should be managed with multimodality treatment including surgery and radioactive iodine (RAI) [18].

Routine RAI treatment for uncomplicated microPTC is not recommended [18]. According to the European consensus on management of differentiated thyroid cancer there is no benefit in RAI for unifocal microcancers without extension beyond the thyroid capsule or lymph node involvement [22]. There is place for RAI in patients with lymph node or distant metastasis, local invasion, and multifocal disease. However RAI has no proven benefit in reducing the higher recurrence rates associated with multifocal or lymph node positive disease [18].

TSH suppression for patients with micro PTC should be based on the stage of disease and risk of recurrence. For low risk patients a TSH target of 0.1– 0.5 mU/L is suggested and for those with stage III or IV disease TSH should be suppressed below 0.1mU/L [18]. Although there is evidence for benefit of TSH suppression on differentiated thyroid cancer, Noguchi et al. who studied 2070 patients with microPTC found out no increase in recurrent disease in those who discontinued suppressive treatment [23]. The risks of TSH suppression such as osteoporosis in postmenopausal women and cardio-vascular complications in the elderly warrants consideration risks and benefits of treatment rather than routine TSH suppression as advocated by some [24].

There is no role for adjuvant systemic therapy other than RAI and TSH suppression for microPTC as it is a type of differentiated thyroid cancer [5].

Observation without therapeutic intervention has been studied as a management option for microPTC. Ito et al. followed up 340 patients diagnosed with microPTC without adverse features such as unfavorable tumour location, clinically node positive disease and high grade on FNAC. At the end of 10 years 15.9 % had tumour size enlargement of >3mm and 3.4% had new nodal metastasis. Out of 340, 109 (32%) patients underwent thyroidectomy for various reasons during this period and none developed recurrent disease. Patient and clinical characteristics such as gender, age, tumour size at diagnosis, multcentricity or TSH suppression were not associated with enlargement of the lesions [12].

Conclusions

In summary, microPTC of the thyroid is a disease with an excellent prognosis. It is being more commonly diagnosed as a result of liberal use of imaging modalities. Clinicians need to be aware of the natural history and treatment options available including surgery, RAI, TSH suppression and active observation in order to avoid over/under treatment. Association of BRAF proto oncogene mutation with microPTC and its role on determining prognosis and treatment of this disease entity is an ongoing area of research with exciting prospects.

All authors disclose no conflict of interest. The study was conducted in accordance with the ethical standards of the relevant institutional or national ethics committee and the Helsinki Declaration of 1975, as revised in 2000.

References

1. Lloyd R, De Lellis R, Heitz P & Eng C. *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Endocrine Organs* Lyon, France: IARC Press International Agency or Research on Cancer, 2004. doi: 10.1111/cen.12515.
2. Perros P et al. *Guidelines for the management of thyroid cancer,* Third edition. British Thyroid Association, Feb 2014.
3. Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973-2002. *JAMA.* 2006 May 10;295(18):2164-7. doi: 10.1001/jama.295.18.2164.
4. Elio Roti, Ettore C degli Uberti, Marta Bondanelli and Lewis E Braverman. Thyroid papillary microcarcinoma: a descriptive and metaanalysis study. *Eur J Endocrinol.* 2008 Dec;159(6):659-73. doi: 10.1530/EJE-07-0896. *Epub* 2008 Aug 19.
5. Haugen BR et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid.* 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020. Review.
6. Jin J, McHenry CR. Thyroid incidentaloma. *Best Pract Res Clin Endocrinol Metab*. 2012 Feb;26(1):83-96. doi: 10.1016/j.beem.2011.06.004.
7. Hoang JK, Lee WK, Lee M, Johnson D, Farrell S. US Features of thyroid malignancy: pearls and pitfalls. *Radiographics.* 2007 May-Jun;27(3):847-60.

doi: 10.1148/rg.273065038.

8. William D. Drucker, Richard J. Robbins ed., (2006) In: *Practical management of thyroid cancer*. Springer: pp 371-389.
9. Shiva Dideban, Alireza Abdollahi, Alipasha Meysamie, Shokouh Sedghi, Mona Shahriari. Thyroid Papillary Microcarcinoma:Etiology, Clinical Manifestations, Diagnosis, Follow-up, Histopathology and Prognosis. I*ran J Pathol.* 2016; 11(1): 1 – 19.
10. Ito Y, Miyauchi A. A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. *Nat Clin Pract Endocrinol Metab*. 2007 Mar;3(3):240-8. Review.
doi: 10.1038/ncpendmet0428.
11. Sak SD. Variants of Papillary Thyroid Carcinoma: Multiple Faces of a Familiar Tumor. *Turk Patoloji Derg*. 2015;31 Suppl 1:34-47.
doi: 10.5146/tjpath.2015.01313.
12. Ito Y et al. An observational trial for papillary thyroid microcarcinoma in Japanese patients. World J Surg. 2010 Jan;34(1):28-35.
doi: 10.1007/s00268-009-0303-0.
13. So Y K, Kim M W, Son Y I. Multifocality and bilaterality of papillary thyroid microcarcinoma. *Clin Exp Otorhinolaryngol*. 2015 Jun;8(2):174-8.
doi: 10.3342/ceo.2015.8.2.174.
14. Wada N et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. *Ann Surg*. 2003 Mar;237(3):399-407.
doi: 10.1097/01.SLA.0000055273.58908.19.
15. Young Don Lee. Surgical Strategy for Papillary Thyroid Microcarcinoma. *J Korean Thyroid Assoc* 2014 May 7(1): 48-56.
doi.org/10.11106/jkta.2014.7.1.48.
16. Jin-Kyu Cho et al. Clinical features and prognostic factors in papillary thyroid microcarcinoma depends on age. *J Korean Surg Soc* 2012;82:281-287.
doi: 10.4174/jkss.2012.82.5.281.
17. Robert I Haddad. *NCCN Clinical Practice Guidelines in Oncology.* Thyroid carcinoma. Version 1.2016.
18. Bernet V. Approach to the patient with incidental papillarymicrocarcinoma. *J Clin Endocrinol Metab.* 2010 Aug;95(8):3586-92.
doi: 10.1210/jc.2010-0698.
19. Chow SM et al. Papillary microcarcinoma of the thyroid-Prognostic significance of lymph node metastasis and multifocality. *Cancer.* 2003 Jul 1;98(1):31-40.
doi: 10.1002/cncr.11442.
20. Chan AC, Lang BH, Wong KP. The pros and cons of routine central compartment neck dissection for clinically nodal negative (cN0) papillary thyroid cancer. *Gland Surg.* 2013 Nov;2(4):186-95.
doi: 10.3978/j.issn.2227-684X.2013.10.10.
21. Caliskan M, Park JH, Jeong JS, Lee CR, Park SK, Kang SW, Jeong JJ, Chung WY, Park CS. Role of prophylactic ipsilateral central compartment lymph node dissection in papillary thyroid microcarcinoma. *Endocr J.* 2012;59(4):305-11. Epub 2012 Jan 12.
22. Furio Pacini et al. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. *European Journal of Endocrinology* (2006) 154 787–803.
doi: 10.1530/eje.1.02158.
23. Noguchi S, Yamashita H, Uchino S, Watanabe S. Papillary microcarcinoma. *World J Surg. 2*008 May;32(5):747-53.
doi: 10.1007/s00268-007-9453-0.
24. Sakorafas GH, Giotakis J, Stafyla V. Papillary thyroid microcarcinoma: a surgical perspective. *Cancer Treat Rev.* 2005 Oct;31(6):423-38. Epub 2005 Jul 6.
doi: 10.1016/j.ctrv.2005.04.009.
25. M Xing. BRAF mutation in thyroid cancer. *Endocrine-Related Cancer* (2005) 12 245–262. Review.
doi: 10.1677/erc.1.0978.
26. Melck AL, Yip L, Carty SE. The utility of BRAF testing in the management of papillary thyroid cancer. *Oncologist*. 2010;15(12):1285-93.
doi: 10.1634/theoncologist.2010-0156.