

## Lymph node metastasis in thyroid papillary microcarcinoma: a study of 170 patients

R VARSHNEY, M N PAKDAMAN, N SANDS, M P HIER, L ROCHON, M J BLACK,  
R J PAYNE

McGill University, Department of Otolaryngology – Head and Neck Surgery, Jewish General Hospital, Montreal, QC, Canada

### Abstract

**Objective:** Papillary microcarcinoma of the thyroid has been described as either a normal variant or a serious malignancy. We describe our experience with papillary microcarcinoma and lymph node metastases.

**Method:** A total of 685 consecutive total thyroidectomies with central compartment neck dissection were reviewed for papillary microcarcinoma. Association of central compartment lymph node metastases with age, gender, tumour multifocality, bilaterality and extrathyroidal extension was analysed.

**Results:** Out of 170 papillary microcarcinoma cases, multifocality was found in 72 (42.4 per cent), bilaterality in 49 (28.8 per cent) and extrathyroidal extension in 16 (9.4 per cent). In all, 23 patients (13.5 per cent) had lymph node metastases. There was a significant association ( $p < 0.05$ ) between extrathyroidal extension (but no other tumour characteristics) and lymph node metastases.

**Conclusion:** In all, 13.5 per cent of papillary microcarcinomas in our series showed lymph node metastases. Lymph node metastases were associated with extrathyroidal invasion of the papillary microcarcinoma.

**Key words:** Thyroid Gland; Papillary Thyroid Microcarcinoma; Thyroid Neoplasms; Thyroid Nodule; Lymph Nodes; Neoplasm Metastasis; Neoplasm Invasiveness

### Introduction

Papillary microcarcinoma of the thyroid gland is defined as a papillary carcinoma measuring 1 cm or less in diameter.<sup>1</sup> According to Ito and Miyauchi, these tumours are most commonly discovered in three scenarios.<sup>2</sup> First, incidental microcarcinoma can be found incidentally during the diagnostic evaluation or treatment of other thyroid diseases. Second, occult papillary microcarcinomas can present as metastases to lymph nodes or distant anatomic sites, without an identifiable thyroid mass. Third, latent papillary microcarcinoma can be discovered during autopsy. Autopsy series have reported papillary microcarcinoma incidence rates as high as 36 per cent.<sup>3</sup> There are two philosophies regarding the clinical significance of and approach to treating papillary microcarcinomas: many researchers believe that they are benign and should be treated conservatively,<sup>2,4</sup> while others report serious adverse consequences of papillary microcarcinoma and recommend appropriate treatment.<sup>5–7</sup>

The incidence of lymph node metastasis in papillary microcarcinoma patients varies considerably.<sup>6,8</sup> Distant metastases to bone, lungs and brain have also been reported.<sup>6–12</sup> In an autopsy series, lymph node

metastases were found in 3.1–18.2 per cent of cases.<sup>6</sup> In surgical series, rates of 13.5–64.1 per cent have been reported.<sup>2,13</sup>

Although it is evident from these studies that papillary carcinomas less than 10 mm in diameter can metastasise to lymph nodes,<sup>6,8</sup> little is known about which specific tumour characteristics confer a greater risk of regional spread. Studies have shown lymph node metastasis of papillary microcarcinomas to be associated with tumour multifocality,<sup>6,8,13–15</sup> tumour size,<sup>14,16</sup> patient age<sup>17</sup> and extrathyroidal invasion.<sup>14,15,17</sup> However, there are contradictory reports about which clinical and histopathological characteristics predict locoregional spread. This study aimed to (1) determine the incidence of lymph node metastasis in papillary microcarcinoma cases at a major university teaching hospital and (2) elucidate which papillary microcarcinoma characteristics are associated with lymph node involvement.

### Methods

A retrospective review of 685 consecutive patients who underwent total thyroidectomy for both benign and malignant disease between January 2006 and

December 2012 was performed by an experienced thyroid surgeon at a McGill University teaching hospital in Montreal, Canada. From 2006 onwards, all patients who underwent total thyroidectomy also underwent a modified central compartment neck dissection, regardless of pre-operative fine needle aspiration cytology (FNAC), to ensure the removal of any occult metastasis. This was done to avoid the increased morbidity associated with central neck dissection at a later date. Our investigation was approved by the hospital's Research Ethics Committee. An experienced thyroid cancer pathologist reviewed all histological specimens.

Patients were included if a papillary microcarcinoma was identified in a thyroid specimen. Diagnoses were made according to the World Health Organization Classification of Thyroid Tumors,<sup>1</sup> which defines papillary microcarcinoma as a lesion less than or equal to 10 mm in diameter, with no previous suspicion that the lesion is malignant. Patients with concurrent papillary carcinomas larger than 10 mm were excluded to ensure that all cases of lymph node metastasis resulted from extension of a papillary microcarcinoma. Patient demographics, tumour characteristics and central compartment lymph node status were noted.

#### Statistical analysis

We evaluated the influence of gender, patient age, tumour multifocality, presence of thyroid capsular invasion and tumour bilaterality on lymph node metastasis. To identify the clinical and histopathological variables affecting lymph node metastasis, the one-tailed Fisher's exact test was used for univariate analysis. A *p* value of less than 0.05 was considered significant. Results are expressed as mean  $\pm$  standard deviation.

#### Results

The mean age of the 685 patients reviewed in this study was  $53.62 \pm 12.47$  years (range 20–91 years). A total of 162 had benign disease, 353 had a non-papillary microcarcinoma malignancy and 170 had papillary microcarcinoma without a simultaneous papillary thyroid carcinoma less than 10 mm in size. The study population mainly consisted of females (84.7 per cent) and 65.3 per cent were older than 45 years. Of the suitable 170 patients, 72 (42.4 per cent) harboured multifocal disease and 28 (16.5 per cent) had bilateral tumours. Extrathyroidal extension of papillary microcarcinoma was present in 16 patients (9.4 per cent; Table I).

Furthermore, 23 patients (13.5 per cent; 4 males and 19 females) had central compartment lymph node metastases. Of these, 11 patients were aged 45 years or younger and 12 were older. Eleven patients had tumours that extended beyond the thyroid capsule, 12 had multifocal tumours and 7 had bilateral tumours (Table II).

TABLE I  
CHARACTERISTICS OF PAPILLARY MICROCARCINOMA PATIENTS

PMC characteristics	Patients (n (%))
Age	
≤45 years	59 (34.7)
>45years	111 (65.3)
Gender	
Male	26 (15.3)
Female	144 (84.7)
Multifocality	
Unifocal	98 (57.6)
Multifocal	72 (42.4)
Bilaterality	
Unilateral	142 (83.5)
Bilateral	28 (16.5)
Extracapsular invasion of thyroid	
No invasion	154 (90.6)
Invasion	16 (9.4)

PMC = papillary microcarcinoma

Associations between lymph node metastasis and gender, age, papillary microcarcinoma bilaterality and papillary microcarcinoma multifocality were not statistically significant (*p* > 0.05). In contrast, thyroid capsule invasion correlated significantly with lymph node metastasis (*p* = 0.0001).

#### Discussion

The incidence of papillary microcarcinoma is increasing in North America. Many authors attribute this finding to an increased detection of subclinical disease resulting from improved imaging techniques, rather than an actual increase in thyroid cancer incidence.<sup>7,15,18</sup> Our group previously reported a papillary microcarcinoma rate of 49.9 per cent in a cohort of more than 800 thyroidectomy patients.<sup>19</sup>

TABLE II  
CHARACTERISTICS OF PATIENTS WITH LYMPH NODE METASTASES

Characteristics	Patients* (%)	<i>p</i> value
Age		
≤45 years	11/59 (18.6)	0.1188
>45years	12/111 (10.8)	
Gender		
Male	4/26 (15.4)	0.4825
Female	19/144 (13.2)	
Multifocality		
Unifocal	11/98 (11.2)	0.2117
Multifocal	12/72 (16.7)	
Bilaterality		
Unilateral	16/142 (11.3)	0.0569
Bilateral	7/28 (25.0)	
Extracapsular invasion of the thyroid		
No invasion	12/154 (7.8)	0.0001
Invasion	11/16 (68.8)	

\*Number of patients with lymph node metastases out of the total number of papillary microcarcinoma patients with that particular characteristic. *p* < 0.05 is considered statistically significant

There is considerable controversy regarding the most appropriate management of these tumours. Burman claims that the lack of long-term controlled data means that any suggested approach is, to a certain extent, simply an opinion.<sup>20</sup> Prospective clinical trials to determine the optimal approach for papillary microcarcinoma management are difficult because, by definition, papillary microcarcinomas are incidental findings.<sup>15,21</sup> Previously, Ito *et al.* followed papillary microcarcinoma patients who chose observation with serial ultrasound over surgical management, and showed reduction or no change in tumour growth in 70 per cent over an average of 46 months.<sup>22</sup> However, they also reported an incidence of lymph node metastasis greater than 50 per cent in patients who chose surgical management. It is firmly established that papillary microcarcinoma can metastasise to both lymph nodes and distant regions of the body.<sup>6–8,13,15–17</sup> Thus, more definite management guidelines for papillary microcarcinoma patients, comprising routine follow up with ultrasound or surgical management, must be established.

We report a 13.5 per cent overall incidence of central compartment lymph node metastasis in patients with papillary microcarcinoma without concomitant papillary carcinoma who underwent central neck dissection. Lymph node metastasis rates of 3.1–18.2 per cent in autopsy studies and of 13.5–64.1 per cent in surgical series have been reported.<sup>2,6</sup> A strength of our study is the high degree of certainty regarding the incidence of lymph node metastasis because all patients undergoing total thyroidectomy also underwent central neck dissection.

There is growing interest in determining which clinical and histological characteristics of papillary microcarcinoma are associated with lymph node metastasis. We did not find a statistically significant effect of gender or age on lymph node involvement. However, some authors have reported a significantly increased risk in men compared with women,<sup>14</sup> and in patients aged over 45 years.<sup>17</sup>

- **Papillary microcarcinoma of the thyroid gland is an incidental finding of papillary carcinoma measuring 1 cm or less in diameter**
- **It is unclear which characteristics of papillary microcarcinoma predict lymph node metastasis**
- **We report a 13.5 per cent overall incidence of central compartment lymph node metastases in patients with papillary microcarcinoma**
- **For isolated papillary microcarcinoma without concomitant papillary carcinoma, thyroid capsule invasion is the only characteristic to correlate with lymph node metastasis**

Previous studies identified multifocality as a prognostic factor for lymph node metastasis.<sup>6,8,13–15</sup> Furthermore, increased aggressiveness has been reported for bilateral papillary microcarcinoma. Pellegriti *et al.* demonstrated that bilateral papillary microcarcinoma can be a strong prognostic indicator of persistent or recurrent disease.<sup>17</sup> However, although bilateral disease was associated with a trend towards a higher percentage of lymph node metastasis, this was not statistically significant in our study.

Thyroid capsule invasion of papillary microcarcinoma is reported to be associated with lymph node metastasis.<sup>14,15,17</sup> Our study clearly demonstrates that in a large cohort of isolated papillary microcarcinoma patients without concomitant papillary carcinoma, thyroid capsule invasion is the only characteristic to correlate with lymph node metastasis. In our series of 170 patients, nearly 70 per cent of those with capsule invasion had lymph node metastases, whereas less than 10 per cent of those without capsule invasion had lymph node metastases.

## Conclusion

Studies such as ours should provide clinicians with the tools to more objectively predict which patients may develop lymph node metastases. In cases with thyroid capsule invasion, additional cautionary measures should be added to the current recommendations for managing these tumours when central compartment dissection has not been undertaken during surgery. For instance, post-surgical ultrasonographic assessment and follow up of neck lymph nodes by a dedicated neck ultrasound specialist should be strongly encouraged. Standard management of suspicious lymph nodes, comprising FNAC and thyroglobulin measurement on needle washout, followed by surgical removal if positive, should follow. Furthermore, in selected cases, addressing the central compartment lymph nodes would essentially require a second operation regardless of imaging findings. In other cases, thyroid-stimulating hormone suppression and regular follow up with thyroglobulin may be all that is necessary.

## References

- 1 Hedinger C, Williams ED, Sobin LH. The WHO histological classification of thyroid tumors: a commentary on the second edition. *Cancer* 1989;**63**:908–11
- 2 Ito Y, Miyauchi A. A therapeutic strategy for incidentally detected papillary microcarcinoma of the thyroid. *Nat Clin Pract Endocrinol Metab* 2007;**3**:240–8
- 3 Pazaitou-Panayiotou K, Capezzone M, Pacini F. Clinical features and therapeutic implication of papillary thyroid microcarcinoma. *Thyroid* 2007;**17**:1085–92
- 4 McDougall R, Camargo CA. Treatment of micropapillary carcinoma of the thyroid: where do we draw the line? *Thyroid* 2007;**17**:1093–5
- 5 Pelizzo MR, Boschin IM, Toniato A, Piotto A, Bernante P, Pagetta C *et al.* Papillary thyroid microcarcinoma (PTMC): Prognostic factors, management and outcome in 403 patients. *Eur J Surg Oncol* 2006;**32**:1144–8
- 6 Chow SM, Law SCK, Chan JKC, Au SK, Yau S, Lau WH. Papillary microcarcinoma of the thyroid—prognostic

- significance of lymph node metastasis and multifocality. *Cancer* 2003;**98**:31–40
- 7 Roti E, Rossi R, Trasforini G, Bertelli F, Ambrosio MR, Busutti L *et al.* Clinical and histological characteristics of papillary thyroid microcarcinoma: results of a retrospective study in 243 patients. *J Clin Endocrinol Metab* 2006;**91**:2171–8
  - 8 Baudin E, Travagli JP, Ropers J, Mancusi F, Bruno-Bossio G, Caillou B *et al.* Microcarcinoma of the thyroid gland: the Gustave-Roussy Institute experience. *Cancer* 1998;**83**:553–9
  - 9 Fend F, Gruber U, Fritzsche H, Rothmund J, Breittfellner G, Mikuz G. Occult papillary carcinoma of the thyroid with pulmonary lymphangitic spread diagnosed by lung biopsy. *Klin Wochenschr* 1989;**67**:687–90
  - 10 Michie HR, O'Bryan-Tear CG, Marsh H, Glazer G. Cerebral metastases from occult papillary carcinoma of the thyroid. *Br J Surg* 1987;**74**:647
  - 11 Lin KD, Lin JD, Huang MJ, Huang HS, Jeng LB, Chao TC *et al.* Clinical presentations and predictive variables of thyroid microcarcinoma with distant metastasis. *Int Surg* 1997;**82**:378–81
  - 12 Lin JD, Chen ST, Chao TZ, Hsueh C, Weng HF. Diagnosis and therapeutic strategy for papillary thyroid microcarcinoma. *Arch Surg* 2005;**140**:940–5
  - 13 Wada N, Duh QY, Sugino K, Iwasaki H, Kameyama K, Mimura T *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;**237**:399–407
  - 14 Sampson RJ, Oka H, Key CR, Buncher CR, Iijima S. Metastases from occult thyroid carcinoma. An autopsy study from Hiroshima and Nagasaki, Japan. *Cancer* 1970;**25**:803–11
  - 15 Gülben K, Berberoğlu U, Çelen O, Mersin HH. Incidental papillary microcarcinoma of the thyroid-factors affecting lymph node metastasis. *Langenbecks Arch Surg* 2008;**393**:25–9
  - 16 Kasai N, Sakamoto A. New subgrouping of small thyroid carcinomas. *Cancer* 1987;**60**:1767–70
  - 17 Pellegriti G, Scollo C, Lumera G, Regalbutto C, Vigneri R, Belfiore A. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: study of 299 cases. *J Clin Endocrinol Metab* 2004;**89**:3713–20
  - 18 Davies L, Welch HG. Increasing incidence of thyroid cancer in the United States, 1973–2002. *JAMA* 2006;**295**:2164–7
  - 19 Pakdaman MN, Rochon L, Gologan O, Tamilia M, Garfield N, Hier MP *et al.* Incidence and histopathological behavior of papillary microcarcinomas: study of 429 cases. *Otolaryngol Head Neck Surg* 2008;**139**:718–22
  - 20 Burman KD. Micropapillary thyroid cancer: should we aspirate all nodules regardless of size? *J Clin Endocrinol Metab* 2006;**91**:2043–6
  - 21 Orsenigo E, Beretta E, Fiacco E. Management of papillary microcarcinoma of the thyroid gland. *Eur J Surg Oncol* 2004;**30**:1104–6
  - 22 Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K *et al.* An observation trial without surgical treatment in patients with papillary microcarcinoma of the thyroid. *Thyroid* 2003;**13**:381–7

Address for correspondence:

Dr R Varshney,  
McGill University,  
59 Papillon,  
Dollard-des-Ormeaux,  
QC, Canada H9B3M3

Fax: 001 514 421–5518

E-mail: [rickul.varshney@gmail.com](mailto:rickul.varshney@gmail.com)

---

Dr R Varshney takes responsibility for the integrity of the content of the paper  
Competing interests: None declared

---