

The epidemic of papillary thyroid microcarcinoma: An overview

Abdulaziz A. AlSaif

Department of Surgery, Faculty of Medicine, King Saud University, King Khalid University Hospital, Riyadh, Saudi Arabia

ABSTRACT

According to the World Health Organization, papillary thyroid microcarcinoma (PTmC) is a papillary thyroid cancer (PTC) measuring 10 mm or less in size. There has been a recent worldwide increase in the incidence of thyroid cancer, largely attributed to an increase in the incidence of PTC and more precisely to an increase in the incidence of PTmC. The management of PTmC continues to be an area of controversy and has resulted in wide differences in recommended management, ranging from observation to an aggressive approach with total thyroidectomy, central lymph node dissection and radioiodine ablation therapy. The aim of this review is to present some of the recently published studies discussing the clinical aspects of this disease (PTmC).

Keywords: Epidemic, microcarcinoma, papillary, thyroid

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy.^[1] There has been a worldwide increase in incidence, largely attributed to an increase in the incidence of papillary thyroid cancer (PTC) and more precisely to a huge increase (epidemic) in the incidence of papillary thyroid microcarcinoma (PTmC).^[2-4] Recent studies have shown that the overall increase in the incidence of PTC is partially due to what looks like an epidemic increase in the incidence of PTmC confirmed by more than a 400% increase in incidence reported between 1983 and 2006.^[5,6]

It is not clear if this epidemic increase in the incidence of PTmC is a true increase or due to other factors, such as the more liberal use of imaging modalities especially neck ultrasound for thyroidal and non-thyroidal

conditions,^[2,3] the improved ability of pathologists to detect small and smaller tumours through more rigorous sectioning and studies of surgical thyroid specimens excised for benign conditions. Environmental alterations, irradiation and oncogenic events have also been proposed as contributing factors for this epidemic.^[7-9]

There is a lack of consensus in the way PTmC should be managed: This is largely due to the excellent overall prognosis for this disease. The overall survival for well differentiated thyroid carcinoma exceeds 90% and is even better for PTmC.^[10] The American Thyroid Association (ATA) and the European Thyroid Association (ETA) recommend that the type of the initial surgery and the postoperative care need to be determined depending on the different features of PTmC.^[11,12]

DEFINITION

Microcarcinoma includes many different definitions such as incidentaloma, non-palpable carcinoma, small carcinoma, minimal carcinoma and occult carcinoma.^[13-15] These terms share two meanings: The

Address for correspondence:

Dr. Abdulaziz A. AlSaif, Department of Surgery,
Faculty of Medicine, King Saud University, King Khalid University
Hospital, Riyadh, Saudi Arabia.
E-mail: aalsaif@ksu.edu.sa

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small tumour size and the non-clinical mode of tumour presentation. Recently, the term (microcarcinoma) has almost replaced all the previous definitions. Since almost all these tumours are of papillary type, the preferred definition is now micropapillary thyroid carcinoma.^[16,17]

INCIDENCE

Harach *et al.*, reported that the prevalence of PTmC in an autopsy series was 36% among 101 autopsies.^[15] Other autopsy studies reported a prevalence as low as 2.3%.^[18,19] There are many autopsy series in the literature reporting PTmC prevalence in between these two figures. The wide range in the reported prevalence (2.3 – 36%) is probably in part due to different methodological approaches, the histopathological criteria used to diagnose PTC and geographic differences.^[20,21] Incidental foci of PTmC were found in a large percentage of patients after thyroidectomy for a presumably benign thyroid conditions, ranging from 2 - 24%.^[22,23]

NATURAL HISTORY OF PAPILLARY THYROID MICROCARCINOMA

Noguchi *et al.*, reported 2,070 patients with PTmC observed over a 30-year period, and there was a strong female preponderance. The factors that influenced recurrence of PTmC were: Age more than 55 years and tumour size. PTmC was divided into tumours 1 – 5 mm and 6 – 10 mm with the smaller tumours having a more favourable recurrence free survival rate at 35 years. Patients with grossly involved cervical lymph nodes were more likely to have recurrences. Patients with no lymph node metastases were compared with patients who did not have a lymph node dissection; the result was no difference in recurrence rate. Overall, the recurrence rate was 3.5% with a median time to recurrence of 10.3 years. The majority of recurrences were locoregional. Distant recurrences occurred in 0.6% of patients. The mortality rate was extremely low, 12 deaths (0.6%) during a follow-up period of 16.5 ± 7.3 years.^[24]

Hay *et al.*, reviewed 900 patients diagnosed with PTmC over a period of 60 years, the mean follow-up time was 13.5 years. At the time of diagnosis, 30% had lymph nodes metastases, 2% had extrathyroidal extension and 0.3% had distant metastases. 17% had postoperative radioiodine remnant ablation therapy (RRA), 85% had total or near total thyroidectomy. There was no significant difference in the overall survival between patients with PTmC and the normal population. Twenty and 40 year recurrence rates were 6% and 9%, respectively. After

20 years, recurrence in the thyroid bed was 2%, while recurrence in the regional lymph nodes was 5% and there were no distant recurrences. Patients with multifocal tumour and positive lymph nodes were having higher recurrence rates. Lobectomy did not increase the recurrence rate. There was also no survival advantage offered by RRA. This study confirmed the excellent prognosis of PTmC.^[25]

PRESENTATION AND DIAGNOSIS

The mean age at diagnosis of patients with PTmC has been reported by different studies to be 41.9 – 48.5 years, it is much more common in females compared to males 82.6:17.4.^[5,26]

PTmC is typically without any symptoms, being seen either during autopsy, or incidentally found in the histopathology of a gland removed for benign conditions, or found during neck ultrasound for different reasons, which is the most frequent presentation, or in the unlikely situation of a clinically palpable thyroid mass, or rarely present with locoregional/distant metastases. The average size of PTmC is about 6 mm.^[25] Multiple foci of PTmC may be limited to one lobe or both. Multi-focality is found in 30 – 40% of cases and bilaterality in approximately 20%.^[27,28]

Neck ultrasound is the mainstay for imaging to detect thyroid and cervical lymph node pathology; it is an extremely sensitive and cost-effective method.^[29-31]

Ultrasound-guided fine needle aspiration biopsy has greatly increased the frequency of preoperative diagnosis of thyroid cancer.^[32] It has a relative sensitivity of 60 – 90%, specificity of 100%, a positive predictive value of 100%, a negative predictive value of 80% and accuracy of 85% for diagnosing thyroid cancer.^[20]

PROGNOSIS AND PROGNOSTIC FACTORS

The overall survival for well-differentiated thyroid carcinoma including PTC is more than 90%, and it is even better for PTmC.^[10] Yu *et al.*, analysed 18,445 cases of PTmC, the 10-year and the 15-year overall survival for PTmC were reported to be 95% and 91%, respectively. The 10-year disease-specific survival was approximately 99.5%.^[33] Having said that, it is known that PTmC is not a homogenous disease and consequently, risk-stratification models have been developed to identify high-risk patients who will need more aggressive treatment and close, long-term follow-up. Table 1 shows the prognostic scoring systems for PTC which are commonly used in clinical practice.^[34]

Table 1: Prognostic scoring systems for papillary thyroid cancer

Centre where the system was developed	Scoring system	Year of publication
MSKCC	GAMES: Grade, age, distant metastasis, extrathyroidal extension, size	1992
Mayo Clinic	AGES: Age, grade, extrathyroidal extension, size	1987
	MACIS: Distant metastasis, age, completeness of resection, invasion, size	1993
Lahey Clinic	AMES: Age, distant metastasis, extrathyroidal extension, size	1988
Karolinska Hospital and Institute	DAMES: DNA ploidy, age, distant metastasis, extrathyroidal extension, size	1992

MSKCC: Memorial Sloan-Kettering Cancer Center

PATIENT'S AGE

Yu *et al.*,^[33] reported that patients >45 years showed a much worse survival with an overwhelmingly high hazard ratio of 6:18, which made age to be the most powerful prognostic factor among all factors analysed. Gender is not included as a risk factor in almost all the well-known scoring systems.^[34]

TUMOUR SIZE

The average size of PTmC is 5 – 6 mm,^[35] however, Pellegriti *et al.*, categorized tumours according to size: <10 mm and 11 – 15 mm, the larger the tumour size, the more chances of finding signs of aggressiveness, this was more evident for tumours larger than 10 mm as opposed to tumours <10 mm in size. Signs of aggressiveness included multifocality, bilaterality, extrathyroidal extension and cervical lymph nodes metastases.^[36]

TUMOUR MULTIFOCALITY

Although PTmC is often multifocal at presentation in 20 – 46% of patients,^[35,37] yet multifocality is not considered as a prognostic factor in any of the current scoring systems for PTC.^[34] Having said that, Baudin *et al.*, reported that the recurrence rate for patients with unifocal PTmC was 1.2% compared with 8.6% for patients with multifocal PTmC, also they noted that the recurrence rate after total thyroidectomy was 2.3% compared to 8.2% after lobectomy and isthmectomy.^[27]

EXTRACAPSULAR INVASION

The invasion of tumour through the thyroid capsule is an important risk factor and has been incorporated into all the prognostic scoring systems for PTC,^[34] it's occurrence ranges from 2 - 21%, this wide variation

may be explained by the location of the PTmC within the thyroid lobe itself.^[25,35]

LYMPH NODES METASTASIS

When PTmC patients have palpable cervical lymph nodes at presentation, their chances of having future lymph node recurrence is high, in the range of 11 - 22% compared to 0.8 - 6% for node negative patients.^[25,38] Chow *et al.*, reported an eleven-fold increase in the risk of distant metastases with the presence of cervical lymphadenopathy.^[28] Therapeutic lymph node dissection should be performed to patients having clinically palpable cervical nodes.

DISTANT METASTASIS

This is a rare occurrence. Three studies on patients with PTmC, reported the rate of distant metastasis to be between 0.2 - 2.85%.^[11,27,28] Patients with PTmC and distant metastasis have a significantly worse prognosis compared to patients who do not have distant metastasis. These patients should be aggressively treated by all treatment modalities available.

GENETICS

Many studies have shown the association between the v-raf murine sarcoma viral oncogene homolog B1 (BRAF) valine-to-glutamic acid mutation at codon 600 (V600E) (BRAF^{V600E}) and aggressive pathological features of PTC, the risk of cancer recurrence and tumour related mortality.^[39] Niemeier *et al.*, analysed a group of patients with aggressive PTmC selected on the basis of lymph node involvement or tumour recurrence, they compared this group with another group of PTmC who were having non-aggressive tumours. They detected BRAF^{V600E} in 77% of the aggressive group, but in 32% of the non-aggressive group, suggesting that the V600E mutation may be a marker of invasiveness and together with the pathological features of aggressiveness, may allow for PTmC clinical risk stratification.^[40]

THE AGGRESSIVE PAPILLARY THYROID MICROCARCINOMA

Page *et al.*, published a series of 41 cases. These cases were considered to be aggressive because of the presence of several risk factors such as, tumour size of more than 5 mm, multifocality, capsular invasion, vascular emboli, tumour extension and metastatic lymphadenopathy. All patients had total thyroidectomy, cervical node dissection and radioiodine (¹³¹I) treatment. They observed no recurrence at all in this subgroup over a period of follow-up ranging from 6 months to 8 years.^[41]

FAMILIAL PAPILLARY THYROID MICROCARCINOMA

Roti *et al.*, documented several studies in the literature where PTmC was observed in members of the same family, representing an overall prevalence of 4.5% of all PTmC cases.^[42] One of these studies reported that familial PTmC is more aggressive than non-hereditary types, however, this finding was not confirmed by other studies,^[43] most likely due to the fact that familial PTC consists of different syndromes with a heterogeneous genetic susceptibility to thyroid cancer.^[42]

RISK FACTORS FOR THE PRESENCE OF OCCULT CENTRAL LYMPH NODE METASTASIS IN CLINICALLY NODE NEGATIVE PATIENTS

Most of the central lymph node metastases are < 5 mm.^[44] The sensitivity of ultrasound in detecting central lymph node metastases is approximately 40%.^[45] Wada *et al.*, reported a series of 259 PTmC patients who had a thyroidectomy and lymph node dissection at the same time, they observed that, up to 64% of them had central node metastases.^[46] It seems that there are certain clinical and pathological features associated with a higher frequency for finding positive central lymph nodes, such as male gender, age <45 years, large tumour size (more than 6 mm), bilaterality, multifocality, extracapsular spread and tumours located at lower third of the gland.^[47]

MANAGEMENT

PTmC has high rates of bilateral disease, multifocality and lymph nodes involvement.^[48-50] On the other hand, it has excellent recurrence-free rates and overall survival.^[28] This picture led to a lot of debate about the appropriate treatment of the disease. Recommendations ranged from observation to more aggressive treatment (total thyroidectomy, lymph node dissection and radioiodine ablation therapy).^[51,52] In general, the great majority of the literature supports a disease-extent based approach. The ATA and the ETA recommend surgery as the initial treatment of PTmC.^[11,12]

The ATA recommend lobectomy alone for small (<10 mm), low risk, unifocal, intra-thyroidal papillary carcinoma in the absence of prior head and neck irradiation for clinically or radiologically involved cervical lymph nodes, the same recommendation applies in relation to the need for complete thyroidectomy for incidentally found PTmC following a previous thyroid lobectomy; on the other hand, total thyroidectomy is recommended for multifocal PTmC or in cases with lymph node metastases.^[11]

Prophylactic central compartment neck dissection in patients with clinically uninvolved central neck lymph nodes is not recommended by the ATA guidelines for the majority of cases, unless there is a gross extrathyroidal extension of the primary tumour.^[11]

On the other hand, it has been suggested that prophylactic central lymph node dissection is indicated because of the high rate of involved lymph nodes at diagnosis, inaccuracy of ultrasound in detecting central compartment nodal involvement and the high complication rates in patients needing reoperation to deal with local recurrence.^[53]

Ito *et al.*, reported their experience with 910 patients diagnosed with PTmC. All patients were offered observation or surgery, 340 patients opted for observation and were followed-up for 15 years. During follow-up, the size of their tumours increased by 3 mm or more in 6.4% of cases at 5 years and 15.9% at 10 years, other tumours remained stable. Novel nodal metastasis was detected in 1.4% of cases at 5 years and in 3.4% at 10 years. During follow-up, 56 patients were referred for surgery, and the histopathological features of the tumours in those 56 patients were not different from that seen in patients who opted to go for surgery at diagnosis, suggesting that delaying surgery does not harm the final outcome. They concluded that PTmC which is not associated with unfavourable features can be a candidate for observation.^[52,54]

As mentioned before, the rate of multifocality in PTmC is high. Other lobe involvement in patients initially thought to have unifocal disease before performing total thyroidectomy is as high as 15 – 20%.^[27,36] The recurrence rate for patients with multifocal disease who had total thyroidectomy was between 2.3% and 5%, but it was between 8.2% and 25% for those who had lobectomy.

Ross *et al.*, analysed the data of 611 PTmC patients for recurrence, depending on the extent of surgery and the use of radioactive iodine (RAI), they concluded that patients with multifocal PTmC had a reduced risk of recurrence after total or near total thyroidectomy compared with less surgery.^[38]

To conclude, and based on the above studies, total or near total thyroidectomy might be the preferred initial surgical strategy for most PTmC patients especially in the setting of multifocal lesions which would then help to reduce the recurrence rate of this disease.

The use of postoperative RAI has been a matter of debate. Bonnet *et al.*, have used RAI to reduce recurrence in their patients with residual lymph

node metastases, invasive tumours or aggressive histopathological features.^[55] So *et al.*, reported their experience in treating 551 patients on which they used RAI for their patients with multifocal disease.^[56] It seems that there is a tendency in the literature to use RAI only for high risk PTmC patients. The ATA management guidelines recommend the use of radioiodine in patients with distant metastases or gross extrathyroidal extension.^[11]

SUPPRESSION THERAPY

Suppression of thyroid-stimulating hormone (TSH) by levothyroxine therapy has been used in the treatment of thyroid cancer for decades. McGriff *et al.*, reported that TSH suppression is associated with a reduced rate of cancer recurrence.^[57] The majority of PTmC patients belong to the low risk category and hence require less aggressive TSH suppression, however, in patients with stage III or IV PTmC, more aggressive suppression might be appropriate. In general, a balance has to be reached between the risk of cancer (progression and recurrence) and the side-effects of suppression which are mainly bone health affection and cardiac side-effects.^[58]

FOLLOW-UP

PTmC patients who had thyroid lobectomy, subtotal or total thyroidectomy, but no RAI ablation should be followed by physical examination of the neck, ultrasound neck, serum thyroglobulin (Tg) levels after levothyroxine withdrawal and Tg antibody levels. The first assessment of the Tg serum level is very important from a prognostic point of view. Patients having Tg serum level of < 1 ng/ml have a chance of approximately 1% to develop disease recurrence and none developed distant metastases.^[36] The same study showed that the disease relapse rate is 1% and no distant metastases in patients having initial TSH-stimulated Tg level of < 1 ng/ml, but the recurrence rate was 16% for those patients with serum Tg level of 1 – 10 ng/ml and 68% relapse rate seen in patients with a serum Tg level above 10 ng/ml. It is only reasonable to consider patients with undetectable initial stimulated serum Tg levels and negative Tg antibody levels as “cured” and hence need minimal long-term surveillance.

Patients with initial stimulated serum Tg levels > 10 ng/ml may well have a persistent tumour and should be followed-up closely.^[59]

In low-risk patients, the combination of neck ultrasound and serum Tg level measurements have been found to have a sensitivity of 96.3% and a negative predictive value of 99.5%.^[60] An increasing level of Tg during follow-up is a sign of possible disease recurrence.^[61]

CONCLUSION

The world is witnessing a surge in the diagnosis of PTmC, mainly due to the increasing use of neck ultrasound for a variety of reasons and to more diligent histopathological examination of thyroid specimens. In general, PTmC has an excellent prognosis, but there is a small subset that has aggressive behaviour. To date, there is no prospective, randomized, controlled trial to examine if the extent of surgery or postoperative administration of RAI leads to better outcomes in PTmC patients. Total or near total thyroidectomy is the preferred procedure in patients with PTmC in order to deal with tumour multifocality and to decrease overall recurrence rate. Cervical lymph node dissection is only recommended in the presence of cervical lymphadenopathy or T4 cancers. RAI ablation has not been proven to be of benefit in low risk PTmC. In the near future, genetic marker testing may move from the bench to bedside to help in assessing tumour behaviour and tailoring targeted therapies for PTmC patients.

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Conflicts of interest

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