Papillary thyroid microcarcinoma: A surgical perspective

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Summary Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid cancer measuring less than 10 mm in its greatest diameter. It is the most common form of thyroid cancer, detected in up to 36% in autopsy studies. The wide availability and use of neck ultrasonography in the evaluation of carotid arteries and of the thyroid resulted in an increased detection of PTMC. PTMC is often multifocal. The diagnosis is usually based on a combination of clinical examination, laboratory investigations, and specialized radiological techniques (mainly neck ultrasonography combined with fine-needle aspiration cytology). A common scenario is the diagnosis of PTMC as an incidental finding following thyroidectomy for a presumably benign thyroid disease. Despite some controversy, most authors agree that PTMC should be treated by total or near-total thyroidectomy, provided it can be performed safely. Because of its many and major advantages, in our clinical practice, total or near-total thyroidectomy is the procedure of choice for the management of PTMC. Given the high incidence of PTMC as an incidental finding and the frequent multifocality, we also favor total or near-total thyroidectomy for the surgical management of nodular thyroid disease (multinodular goiter or dominant presumably benign thyroid nodule/s). Despite some controversy, we perform central neck lymph node dissection electively, in the presence of cervical lymphadenopathy. Radioiodine ablation therapy may be used as an adjuvant therapy. Prognostic factors (such as tumor multicentricity, positive lymph nodes, capsular or vascular invasion) or scoring systems (such as the AMES) can be used to select patients for radioiodine adjuvant therapy. Suppression therapy is needed after surgical management. Despite the potential for neck lymph node and even distant metastases, the biological behavior of PTMC is in general benign and the prognosis is very good.

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Introduction

Thyroid cancer is the most common endocrine malignancy.\textsuperscript{1} Papillary thyroid microcarcinoma (PTMC) represents a particular variant of papillary thyroid cancer; it is the most common form of thyroid cancer, and usually remains clinically occult.\textsuperscript{2–8} This term (''occult'') has been used in the past for thyroid papillary tumors not exceeding 1.5 cm in size.\textsuperscript{7–19} Evidently, this term indicated the past for thyroid papillary tumors not exceeding 1.5 cm in size. \textsuperscript{7–19} This term (''occult'') has been used in thyroid cancer, and usually remains clinically occult. \textsuperscript{2–8} This term (''occult'' thyroid carcinoma). However, the term ''occult thyroid carcinoma'' was rather confusing.\textsuperscript{11} Subsequently, these lesions have been described under a variety of terms. The maximum size limits varied in the literature (Table 1). Terms used in the past to describe these thyroid tumors included occult thyroid carcinoma, latent papillary carcinoma, small papillary carcinoma, non-encapsulated thyroid tumor, occult sclerosing carcinoma, microcarcinoma, minute/small/tiny thyroid carcinoma, micro-papillary carcinoma, incidentaloma (indicating that the tumor was an incidental finding at autopsy or in thyroidectomy specimens in patients with no clinical suspicion of malignancy).\textsuperscript{6,7,9–12,16,27,31,39–50,57–60} Obviously, such diversity in terminology is confusing.

The advent of improved preoperative diagnostic techniques, and in particular FNAC, usually under ultrasonographic guidance, resulted in an improvement of our ability to detect preoperatively small thyroid tumors, measuring less than 10 mm in maximum diameter, despite being clinically ''occult''.\textsuperscript{7,34} The term ''papillary thyroid microcarcinoma'' (PTMC) has therefore replaced the ''occult'' and others terms used to describe these lesions. Although in the past many investigators used as a cutoff value of 15 mm in diameter to describe ''occult'' thyroid cancer (see above), in the World Health Organization (WHO) monograph on histologic typing of thyroid tumors, PTMC has been defined as ''a papillary carcinoma 10 mm or less in its maximal diameter''.\textsuperscript{5} Currently, this is the generally accepted and most widely used definition of PTMC.

Kasai et al. proposed a further subdivision of PTMC;\textsuperscript{49} the terms ''tiny'' referring to 5–10 mm diameter foci, and ''minute'' for foci of 5 mm diameter or less were suggested because of different incidences of lymph-node metastases (59% vs. 13%) and extrathyroidal extension (10% vs. 3%).\textsuperscript{49} Of note, investigators recently excluded lesions with unusual microscopic appearances, indicating a more aggressive biological behavior, such as invasion of the thyroid capsule, blood or lymphatic vessel infiltration or invasion, or tall cell features.\textsuperscript{61,62} Similarly, tumors detected in children and adolescents under the age of 19 years are also excluded. This exclusion is based on the observation that a significant number of PTMC with a diameter <10 mm occurring in this age group had direct extrathyroidal invasion and may be associated with distant metastases, thereby indicating a different and more aggressive biological behavior compared to the usual PTMC.\textsuperscript{63}

During the 12th Annual Cancer Meeting held at the Institute of Molecular Pathology and Immunology of the University of Porto, Portugal, on March...
3–5, 2003, the term papillary microtumor (PmIT) was recently proposed since it further describes the biological characters and the behavior of this tumor. Indeed this term indicates the fact that this lesion is of small size, that it is a neoplastic disease (remaining purposefully non-committal about its malignant potential, because while the tumor may show microscopic local invasion, it is clinically benign) and that it belongs to the papillary family of thyroid tumors. 

Incidence

Thyroid cancer represents about 1% of all carcinomas. Its incidence in the general population ranges from 0.5 to 10/100.00. It has been estimated that there will be 23,600 new cases of thyroid cancer in the United States in 2004 (Female to male ratio = 2.9/1). Papillary thyroid cancer is the most frequent histological subtype of thyroid cancer, accounting for 85% of cases of thyroid tumors in the US and other iodine-sufficient countries. Its prognosis is good and mortality rate is less than 10%. It is expected that there will be 1460 deaths from thyroid cancer in the US in 2004 (Female to male ratio = 1.35/1).

Data regarding the incidence of PTMC have been published in autopsy and surgical series. The highest reported prevalence of PTMC in autopsy series was 36% among 101 consecutive autopsies by

| Table 1 | Maximum size limits used in the literature to define PTMC |
|---|---|---|
| Reference No. | Author (year) | Terminology used | Maximum size (mm) |
| 40 | David (1992) | Occult papillary carcinoma of the thyroid (PCT) | 10 |
| 9 | Schroder (1984) | Occult PCT | 15 |
| 6 | Tourniaire (1988) | Occult papillary thyroid carcinoma | 10 |
| 41 | Santinini (1996) | Papillary microcarcinoma (PMC) | 10 |
| 7 | Hay (1992) | Occult PCT, PMC | 15,10 |
| 42 | North (1997) | Occult thyroid carcinoma | Case size = 6 mm |
| 43 | Ferrario (1995) | Occult thyroid carcinoma | Case size = 12 mm |
| 10 | Paksoy (1994) | Occult PCT | 15 |
| 11 | Salvadori (1993) | Occult PCT | 15 |
| 44 | Hwang (1992) | Occult thyroid carcinoma | 15 |
| 31 | Yamamoto (1990) | Occult PCT variants | Few mm |
| 45 | Michie (1987) | Occult PCT | Case size = 3 mm |
| 46 | Jancic-Zguricas (1986) | Occult PCT | Case size = 2.4 mm |
| 47 | Mills (1986) | Occult PCT | 15 |
| 48 | Strate (1984) | Occult PCT | 15 |
| 12 | Harach (1984) | Occult PCT | 15 |
| 49 | Kasai (1987) | Small thyroid carcinoma | 0–5 |
| 50 | Bondeson (1981) | Occult thyroid carcinoma | Tiny carcinoma |
| 39 | Fink (1996) | Occult micropapillary carcinoma (MPC) | 10 |
| 51 | Miki (1993) | Small papillary carcinoma of the thyroid | 15 |
| 52 | Kaleem (1996) | PMC | 10 |
| 53 | Rassael (1998) | Microscopic papillary carcinoma of the thyroid | 10 |
| 2 | Hedinger (1988) | Papillary microcarcinoma | 10 |
| 14 | Hubert (1980) | Occult PCT | 10 |
| 54 | Lloyd (1983) | Occult sclerosing carcinoma of the thyroid | 10 |
| 22 | Sakorafas (2004) | Microscopic papillary thyroid cancer | 10 |
| 55 | Falvo (2002) | Papillary microcarcinoma | 10 |
| 56 | Pellegriti (2004) | Small papillary thyroid cancer | 10 |

From Ref. 8, Modified (with permission).

a Occult PCT-NST (Nonsclerosing tumor), NEST (nonencapsulated sclerosing tumor), ET (encapsulated tumor).

b World Health Organization.
Harach et al. from Finland.27 These investigators concluded that "detection of occult papillary thyroid carcinoma is so common in Finland...that they can be regarded as a normal finding". They also proposed that "tumors measuring <5 mm should be considered 'tumor' instead of 'carcinoma' to avoid unnecessary surgeries". Other autopsy studies reported a prevalence ranging from 3% to 35%.16,18,23–33,50,71,72 Most of the autopsy studies did not reveal differences in incidence with respect to gender, age, and thyroid size.17,18

Incidental foci of PTMC were found in a large percentage of patients after thyroidectomy for presumably benign thyroid disease, ranging from 2% to 24%.22,39,52,64,73–75 In the study by Delides et al.,73 of the 11 PTMCs from 611 resected thyroids, six were associated with multinodular goiter, three with toxic adenoma and two with Hashimoto thyroiditis. In our study, in 27 patients with PTMC the disease was associated with multinodular goiter in 21 patients, with follicular adenoma in 6, diffuse hyperplasia of the thyroid in 1, while chronic lymphocytic thyroiditis (Hashimoto) was diagnosed in 4 patients with multinodular thyroiditis.22 Multifocal PTMC in surgical specimens following thyroidectomy is also common (see below).22,39,76,77

The wide range of prevalence in published studies (3–36%) may represent differing thoroughness of thyroid gland sectioning (e.g. the number of sectioning levels), completeness of thyroidectomy, the histologic criteria for diagnosing papillary thyroid cancer, and possible population/geographic differences.34,78 As expected, the highest prevalence (35.6%) was observed by looking at the whole gland in 2–3 mm slices with 4 µm slices of each block, showing that 77% of tumor foci were less than 1 mm in diameter.27 Of note, PTMC ranging in size from 3 to 9.9 mm, which can be detected by ultrasonography, were present in 2.3–5.2% of autopsy studies.27,31,78 Nowadays, it is estimated that PTMC account for up to 30% of all papillary thyroid cancers.34,79 Due to the improvement of imaging methods (mainly ultrasonography), the wide application of screening ultrasonography for the evaluation of thyroid or carotid artery lesions, the use of FNAC (usually under ultrasonographic guidance), and the refinement of pathologic procedures, PTMC is diagnosed with an increased frequency. As previously noted, it has been suggested by some investigators that PTMC should be considered as a normal finding.27 The prevalence of PTMC increases steeply from birth to adulthood and its incidence remains relatively stable afterward.4,26 The appearance of PTMC is rare below the age of 18. It may be possible that this may be due — at least in part — to the fact that young people have little chance to undergo mass screening by neck ultrasonography. Given the differences in incidence that exist between PTMC and clinically detectable papillary thyroid cancer this means that most PTMC tend to remain stable, unless an additional event (e.g. irradiation) occurs causing the tumor to become clinically apparent. Taking into account the frequency of PTMC and the rarity of clinically significant papillary thyroid carcinoma, the chance of this additional event taking place is obviously very low.

When PTMC is detected, it is often multifocal in nature (20–46% of cases) with no clear tendency to be localized to the same thyroid lobe.14,25,27–29,31–33,35,39,50 Interestingly, in a 72-year-old woman, a total of 32 microscopic foci of microcarcinoma were found in the surgical specimen following total thyroidectomy.8 Up to 40% of these patients have neck lymph node involvement28,29,31,50,79 and in 5% of them, lymph node metastases preceded the clinical evidence of the primary tumor.35 In most cases, the lymph node metastases were on the same side as the primary tumor, but nodes have been demonstrated bilaterally and even in the side opposite the primary focus.23 Sampson et al. concluded that lymph node metastases was most often associated with multifocal tumors and tumors with vascular and/or capsular invasion. In addition, the rate of lymph node metastasis was greater than 50% if psammoma bodies were identified within the tumor.23

**Oncogenesis and natural history**

The importance of irradiation in the oncogenesis of papillary thyroid cancer in general and PTMC in particular has been established in many studies. Duffy and Fitzgerald in necropsy study in Hiroshima and Nagasaki following the atomic bombing first recognized the association of head and neck irradiation and the development of carcinoma of the thyroid gland (in most cases PTMC).80 Similarly, in Japan, following the atomic attacks in Nagasaki and Hiroshima, Sampson et al.23 found 536 carcinomas of the thyroid at 3067 autopsies (17.5%) and 97% of these were PTMC; this high incidence of PTMC was observed mainly in persons exposed to 50 cGy or more.23 Wagner et al.51 examined 150 patients who received head and neck irradiation in early life to the thymus, tonsils, or adenoids, or for acne. Almost two-thirds had been irradiated between the ages of 2 and 6 years, with a latent period between irradiation and thyroid surgery of 20–30 years. The total number of thyroid cancers was 48 (32%), of which 13 (27%) were PTMC.
Following the reactor accident at Chernobyl (Ukraine) in April 1986, an autopsy study (on permanent residents of the region of Minsk who died in 1990 and 1991) showed that the incidence of PTMC was 8.8%33 a finding similar to the 9.1% of PTMC reported by Fukunaga and Yatani78 in 1975. This finding is in sharp contrast to the 86% thyroid carcinomas in children living in the Republic of Belarus after the Chernobyl disaster.33 There was a mean interval of 4.4 years between the accident and the detection of these tumors; in this study, only 10 (12%) had a diameter of less than 10 mm (i.e., PTMC). These studies concluded that, although exposure to radiation almost certainly increases the likelihood of developing papillary thyroid cancer, the majority of these tumors will usually be larger than 10 mm (and thus by definition will not be PTMC).34

The high incidence of PTMC found in autopsy studies suggests that most of them have a “benign” behavior.14,23,24,27,28,78,82 The supposition that, with time, PTMC will inevitably increase in size to become a clinically significant thyroid carcinoma is refuted by autopsy studies that showed that the incidence of PTMC did not differ between the different groups depending on age, a finding suggesting that PTMC rarely progresses to clinically apparent thyroid cancer with advancing age. These autopsy studies also revealed that a significant percentage of patients (up to 36%) who died of diseases other than thyroid cancer had PTMC that remained asymptomatic throughout their lives.24,50 The discordance between the prevalence of PTMC and population estimates of death from cancer further support that PTMC is an indolent disease.23,25 For example, Japanese populations have the lowest thyroid cancer mortality rates but one of the highest reports of PTMC.23,83 Therefore, PTMC has a relatively “benign” biologic behavior, grows slowly and usually remains latent, rarely affecting the patient’s life or health.4,24,79

Tumor foci occur with the same frequency in both thyroid lobes and isthmus, and most of them are located near the thyroid capsule. The prognostic significance of tumor size in differentiated thyroid cancer is well known.55,66 Indeed, small papillary thyroid tumors rarely metastasize to distant sites and cancer specific mortality rates are very low (0.4% vs. 7% for tumors ≥15 mm, p < 0.001).66 However, nodal metastases can occur in patients with PTMC21; they have been observed in 4.3% of cases at autopsy in Japan31 and in 14.3% in Germany.28 Other studies found even higher incidence of lymph node metastases in patients with PTMC (up to 40%).79 In the study by Woolner et al. from the Mayo Clinic,15 the smallest tumor focus to metastasize to lymph nodes was 3 mm. In some cases, cervical lymph node metastases preceding the occurrence of the primary tumor may be the first and sole manifestation of the disease.21,84 Lymph-node metastases are most often associated with multi-focal tumors (in 23–33% of patients)7,21,53,85 and tumors with vascular and/or capsular invasion24,86–88 Interestingly, Kasai and Sakamoto49 reported differences in the incidence of nodal metastases and vascular invasion depending on whether the tumor was larger or smaller than 5 mm (see above). However, Rodriguez et al. found no such differences and of note one of their recurrences occurred in a tumor of 4 mm.21 In most cases the lymph-node metastases were on the same side as the thyroid focus, but they can be demonstrated also on the opposite side.23 Cystic metastases in the neck from occult papillary thyroid carcinoma are rarely observed.44,89–91 The presence of lymph node metastases may often not be clinically harmful for the patients, although longer follow-up is necessary to confirm this hypothesis.79 However, the same investigators recently reported that for PTMC the presence of lateral metastasis (detected by ultrasonography) predicts a worse relapse-free survival.92 Although exceptionally rare, distant metastases (vertebral column and other skeletal sites, lungs, etc.) have been reported in patients with PTMC and there have been reports of patients who died of such tumors.12,43,48,66

The association of thyrotoxicosis (Grave’s disease) and thyroid neoplasms measuring less than 15 mm can be observed in 0.3–16% of patients;55,93 this association may probably reflect the role of TSH in the stimulation of tumor growth. Interestingly, those with multifocal tumors had a relatively high incidence of lymphocytic thyroiditis (62%) in the remaining thyroid parenchyma during the definitive histological examination.55

Intrathyroid spread of papillary thyroid cancer has been proposed to explain the coexistence of clinically detectable papillary thyroid cancer and solitary — or more importantly — multifocal PTMC — thereby indicating a more aggressive local spread.94 Similarly, PTMC has been considered by some authors as the earliest form of future large lesions; based on these assumptions, a more rigorous surgical approach has been suggested.94 Clonality studies specifically addressing differences between clinical papillary thyroid cancer with multifocal PTMC or multifocal PTMC alone are still required to support/refute the hypothesis of intrathyroidal spread/metastasis.4
Histology and molecular biology

PTMC are generally well differentiated. They exhibit characteristic architectural, cytological, immunohistochemical, and behavioral features of papillary lesions, such as optically clear of ground glass nuclei, overlapping nuclear arrangements, nuclear grooves, occasionally cytoplasmic invaginations into the nucleus, with distinct marginalization of chromatin.2,8,59,61 A notable difference is the frequent presence of desmoplasia and the superficial location of the tumor close to the capsule of the gland.11 As a result, thyroidal capsular invasion is not unusual. Salvadori et al. observed invasion of the thyroid capsule in 15.2% of patients with PTMC.11 Psammoma bodies are found in the carcinoma in approximately 50% of cases.59 Undifferentiated microscopic thyroid cancer is extremely unusual.95

PTMC most commonly demonstrates RET/PTC1 rearrangements, which have been correlated with tumor characteristics such as lymphatic involvement, indicating a more malignant biologic behavior.96–98 These molecular changes are observed at the early stages of thyroid carcinogenesis, but may be unnecessary for the evolution of the disease.99,100 Many other molecular changes have been described in thyroid cancer (including PTMC).101–103 As in other tumors, thyroid carcinogenesis is a probably a multi-step phenomenon and a number of molecular/genetic changes are required for tumor growth and for the progression of the disease. These molecular/genetic changes may have a prognostic value, since they can be used to predict the biological behavior of the PTMC.4,104

Diagnosis

The diagnosis of PTMC is based on a combination of clinical examination, laboratory investigations, and specialized radiological techniques. PTMC is often clinically undetectable because of its small size and usually remains clinically silent, discovered as an incidental finding at autopsy or in specimens removed for other reasons. However, with the advent of improved methods of diagnostic evaluation (including sophisticated imaging techniques — such as neck ultrasonography — and FNAC), the diagnosis can now often be made preoperatively. It was the recognition of this fact that has led Salvadori et al.11 to question the term “occult”, frequently used in the past to describe PTMC.

The discovery of nodules within the thyroid gland by palpation depends on patient characteris-tics and the experience of the examiner. Thyroid masses with a diameter of 5 mm may be palpated in a patient with a long thin neck, whereas nodules greater than 20 mm may be missed in a short fat neck. Witterick et al.105 showed that, even in experienced hands, 160 (76%) of nodules detected by pathological examination were missed by palpation. Twenty-four of these impalpable tumors were PTMC of median diameter of 3 mm.

Neck ultrasonography (US) is an extremely sensitive and cost-effective method for the detection of thyroid and cervical lymph node pathology.106 The role of other imaging methods in the preoperative diagnosis of PTMC is limited. The prevalence of thyroid nodules in the general population detected by ultrasonography is up to 50%, even for iodine-sufficient regions/countries.107 In endemic goiter regions, this figure is even higher.108 Tumors between 1 and 2 mm in diameter can now be detected with the use of high-resolution transducers.106,109 The advent of FNAC (usually under US-guidance) has greatly increased the frequency of preoperative diagnosis of thyroid cancer, including PTMC.110 We perform FNAC routinely in nodules over 10 mm in diameter; smaller nodules are followed. A more rigorous approach has not been shown to increase survival, and routine FNAC of smaller nodules would not only be a huge burden for health care providers, but would also lead to a substantial number of unnecessary surgeries in patients with false-positive FNAC results or with benign follicular or indeterminate lesions. US-guided FNAC has a relative sensitivity of 60–90%, a specificity of 100%, a positive predictive value of 100%, a negative predictive value of 80%, and accuracy of 85% for the diagnosis of thyroid cancer.34 Specifically regarding PTMC, ultrasound-guided FNAC can diagnose papillary carcinoma in lesions larger than 3 mm.111 By using ultrasound and ultrasound-guided FNAC to screen healthy subjects, Takebe et al.110 and Ishida et al.112 found that 3.5% and 0.14%, respectively, of their patients had small (defined as of diameter 4–20 mm) tumors. The combination of ultrasound and ultrasound-guided FNAC may be diagnostic also in patients who present with enlarged cervical lymph nodes; in this case a preoperative cytological diagnosis can be obtained and the identification of metastatic thyroid cells within these nodes will necessitate thyo-roidectomy. However, diagnosis of thyroid malignancy may be difficult by using H&E staining of the few cells obtained from FNAC.34 Immunohistochemistry using antithyroglobulin antibodies may be particularly helpful, since the follicular cells of the thyroid contain thyroglobulin.113 However, this is a complex, time consuming and expensive laboratory method, thereby limiting its clinical usefulness.
PTMC should not be over-treated. The biologic behavior, it is generally accepted that therapeutic efficacy is difficult. Given its relatively benign associated with PTMC make assessment of therapy difficult. And even thyreroticosis, once thought to be a safeguard against thyroid cancer, may be associated with PTMC (see above, Oncogenesis and Natural History). Rarely, the first manifestation of PTMC may be an enlargement of cervical lymph nodes, detected either clinically or by imaging (usually, ultrasonography). Cervical lymphadenopathy may or may not be associated with clinically palpable or ultrasonographically detectable thyroid nodules. The tumor growth within the lymph node(s) may be rapid, outstretching the blood supply, resulting in liquefaction necrosis and degeneration of the node (see above). The cystic mass is removed with the presumed diagnosis of branchial cyst/branchial cleft anomaly and the diagnosis is established postoperatively following histological examination of the resected cystic lesion. On occasion, finding the thyroid primary responsible for cervical lymph node metastases is difficult, requiring meticulous pathological sectioning. The smallest reported papillary microcarcinoma with a metastasis in a scalene lymph node was 0.2 × 0.3 × 0.6 mm in size and required 1375 sections at intervals of 50 μm. Even more rarely, PTMC may be presented as pulmonary metastases or malignant pleural effusion or other distant metastases. In these cases, the thyroid origin may be shown by positive antithyroglobulin immunohistochemistry and subsequent diagnosis of PTMC is established by thyroid imaging (ultrasonography) and by histology following thyroidectomy.

Treatment

The controversy regarding management of differentiated thyroid cancer (i.e., total thyroidectomy vs. lobectomy and isthmusectomy) exists also in the treatment of PTMC. The low mortality rates associated with PTMC make assessment of therapeutic efficacy difficult. Given its relatively benign biologic behavior, it is generally accepted that PTMC should not be over-treated. The adoption of accurate and universal terminology and an in-depth knowledge of the biological characters and the behavior of PTMC is expected to diminish the percentage of patients who are overtreated and to minimize the psychological anxiety engendered by a diagnosis of "carcinoma". On the other hand, the potential for cure of the patient should not be jeopardized. Appropriate management should achieve the permanent — if possible — cure of the patient; an unacceptably high probability of relapse or even death from a potentially curable disease (i.e., PTMC), because of "under-treatment", should be avoided.

Different therapeutic approaches have been suggested for the management of PTMC.

Surgical management

Management options in the surgical treatment of PTMC include total or near-total thyroidectomy, subtotal thyroidectomy, and lobectomy plus isthmusectomy.

Lobectomy/isthmusectomy

Lobectomy/isthmusectomy is the less aggressive method of surgical management of PTMC. Proponents of the method emphasize the minimal morbidity associated with this procedure, which is performed for a disease with a relatively benign biological behavior. Other investigators proposed lobectomy/isthmusectomy for selected, low-risk patients according to the AGES staging system. It has been reported that lobectomy preserves thyroid function, thereby sparing patients the lifelong need for hormone replacement therapy. However, l-thyroxin therapy is required in 50% of patients immediately after lobectomy and is ultimately required in the majority of them, thereby eliminating this theoretical advantage of lobectomy/isthmusectomy. The high incidence of bilateral or multifocal disease suggests that, even in PTMC, residual tumor may frequently be left behind in the contralateral lobe following lobectomy/isthmusectomy. Locoregional recurrence has been reported in 0–11% of PTMC patients treated by unilateral lobectomy/isthmusectomy. Proponents of lobectomy/isthmusectomy note that typically the recurrence is found in the thyroid remnant or lymph nodes, it is usually characterized by the same minimal risk as the original PTMC, and can be managed by completion thyroidectomy with or without neck lymph dissection. Subtotal thyroidectomy is associated with the same problems and concerns as lobectomy/isthmusectomy in the management of PTMC.
Total/near-total thyroidectomy

Total or near-total (leaving less than 3 g of thyroid parenchyma behind) thyroidectomy is a more radical surgical procedure. Opponents of total or near-total thyroidectomy note the increased risk of complications, mainly hypoparathyroidism and recurrent laryngeal nerve injury. However, in experienced hands, morbidity ranges within acceptable limits; postoperative hypocalcemia, which is usually transient, occurs in only 6% of patients, and recurrent laryngeal nerve injury in about 1%.129 Total or near-total thyroidectomy eliminates the frequently observed multifocal/bilateral disease. This is important, because multifocal thyroid cancer is associated with high relapse rate compared with unifocal cancers,66,130 a characteristic that is true also for PTMC.67 Indeed, total or near-total thyroidectomy is associated with reduced recurrence rates compared with lobectomy/isthmusectomy (5% vs. 20%).87,131 Moreover, performing total or near-total thyroidectomy at the time of diagnosis avoids the risk of reoperation. Although completion thyroidectomy is relatively safe in the hands of an experienced surgeon,132 this procedure may be technically difficult and is associated with a relatively increased risk for the complications (at least twofold);34 obviously, the avoidance of the need for an additional surgical procedure is preferable for both the patient and the surgeon. Finally, total or near-total thyroidectomy offers the possibility of better monitoring of treated patients by scintigraphic scan and thyroglobulin measurements to detect persisting or relapsing disease and it also augments the yield of postoperative radioactive iodine therapy.11,21,55,108 Because of the many advantages, in our clinical practice total/near-total thyroidectomy is the preferred method for the management of PTMC. This procedure can be safely performed, especially in centers with interest and experience in thyroid surgery.

Surgical management of PTMC incidentally discovered following limited thyroid surgery for a presumably benign thyroid disease

The surgical management of PTMC incidentally discovered following a limited thyroid surgery (i.e., lobectomy/isthmusectomy or subtotal thyroidectomy) for presumably benign disease remains a controversial topic. Some investigators have proposed that total (completion) thyroidectomy is not indicated if PTMC is an incidental histological finding, provided that the tumor is TNM stage 1, well-differentiated, and with no enlarged nodes.21 Others have suggested that completion total thyroidectomy with or without neck lymph node dissection should be considered in each case, with prognostic factors taken into account.133 Based on the biological characters of PTMC and to minimize the chance of relapse and eventually death from a potentially curable neoplastic disease, we favor total or near-total (completion) thyroidectomy. Due to the high prevalence of PTMC, we also favor total/near-total thyroidectomy as the procedure of choice during the initial surgery for all nodular thyroid disease (multinodular goiter or dominant presumably benign nodules). Interestingly, Giles et al.134 recently reported a clinical trial of total or near-total thyroidectomy with subtotal thyroidectomy (leaving at least 5 g of thyroid tissue) for patients with euthyroid multinodular goiter in whom malignancy was not suspected. Incidental papillary carcinoma was diagnosed in 8% of their patients; completion thyroidectomy was eventually needed in a small group to enable radioactive iodine ablation. These investigators recommended that total thyroidectomy should be preferred over subtotal to prevent the need for reoperation for patients with incidental PTMC. This seems particularly reasonable because other groups have previously reported a risk for benign contralateral nodule growth requiring reoperation after lobectomy for nodular goiter.128,135 Surely, this is the clinical experience of many endocrine surgeons.

Neck lymph node dissection

Although some authors have suggested routine central neck lymph node dissection in patients with non-incidental PTMC,115 we do not perform prophylactic lymph node dissection and we support a more selective approach, especially when postoperative radiiodine ablation therapy is planned. This is the standard of care in the management of thyroid cancer, including PTMC.107 Lymph node dissection is generally indicated when there is cervical lymphadenopathy detected either preoperatively or intraoperatively. In this case, central lymph node dissection should be performed at the time of thyroid surgery (total or near-total thyroidectomy), since subsequent surgery for node metastases in the neck may be technically difficult. Some investigators have suggested simple excision of involved lymph nodes ("berry picking procedure");7,131 however, the "berry picking procedure" is generally considered as inappropriate because it is associated with a higher incidence of regional recurrence when compared with central or modified neck dissection.136 Central (usually) or modified lymph node dissection (when there is more extensive neck lymphadenopathy) yields useful information about the extent of tumor in PTMC. The surgeon should keep in his/her mind that neck
lymph nodes are the main site of locoregional recurrence in PTMC — albeit rare (~1.6%). Involvement of neck lymph nodes is strongly related to multifocality.\textsuperscript{7,24,87,88}

\section*{Radioiodine ablation therapy}

Radioactive iodine therapy may be indicated for selected patients after total or near-total thyroidectomy.\textsuperscript{7,34,77} In our practice, we rely on established prognostic factors (such as tumor multicentricity, positive lymph nodes, capsular or vascular invasion) or prognostic scoring systems (such as the AMES) to select patients for radioiodine therapy. Radioiodine ablation therapy may improve recurrence rates and facilitate postoperative follow-up by measuring serum thyroglobulin concentrations. However, others have reported that radioiodine therapy had no significant effect regarding recurrence rates for PTMC.\textsuperscript{35,77}

\section*{Suppression therapy}

Routine use of thyroxine to suppress TSH secretion is recommended in the management of PTMC.\textsuperscript{34}

\section*{Observation alone}

Although surgery has a key role in the management of PTMC, some authors have suggested an elective surgical management of selected patients; a significant proportion of patients with PTMC — according to these authors — can be managed by observation alone or by suppression therapy. This approach is based on the relatively benign biological behavior of PTMC. As previously noted, investigators from Finland have suggested that PTMC should be considered as a normal finding\textsuperscript{27} and they further recommended that, in practice, detection of a small PTMC without regional metastases should not lead to any treatment. In another interesting study from Japan, 162 patients with PTMC (diagnosed by ultrasonography and FNAC) were treated by observation alone. Levothyroxine was administered to 11 patients to suppress the thyroid-stimulating hormone as the patient’s choice. This group of patients represented 162/732 (22%) of the total number of patients with PTMC (the other patients preferred surgery). Mean follow-up was 46.5 ± 21.5 months. During this period, more than 70% of tumors in the observation group either did not change or decreased in size compared to their initial size at the time of diagnosis. They enlarged by more than 10 mm in 10.2% of patients and lymph node metastases in the lateral compartment appeared in only 1.2% of patients during the follow-up. On the other hand, 570 patients chose surgical treatment at diagnosis and 56 patients in the observation group who underwent surgery after a period of follow-up were classified as the surgical treatment group. Of these 626 patients, lymph node dissection was performed in 594 patients, and metastasis was confirmed histologically in 50.5%. Multiple tumor formation was seen in 594 patients and metastasis was confirmed histologically in 50.5%. Multiple tumor formation was seen in 42.8% of patients. In this group, recurrence rate was 2.7% at 5 years and 5% at 8 years following surgery. The authors concluded that PTMC do not frequently become clinically apparent, and that patients can choose observation alone, while their tumors are not progressing, although they are pathologically multifocal and involve lymph nodes in high-incidence. The authors recommend that surgery should be reserved for PTMC with unfavorable features (such as tumors located adjacent to trachea, tumors possibly invading the recurrent laryngeal nerve, FNAC findings suggesting high-grade malignancy, and lymph nodes highly suspicious of metastases or confirmed as metastasis by FNAC in the lateral compartment and detected by ultrasonography). According to these investigators, it is usually not late for surgeons to recommend surgical treatment when tumors show apparent progression. However, they recognize that further studies with a longer follow-up and with a large number of patients are needed to confirm these recommendations. We believe, however, that once "carcinoma" (including PTMC) is detected — most patients, at least in our country, would prefer surgery to observation or suppression therapy alone. We have not experience with this type of management of PTMC (observation alone). Patients with significant co-morbidities or refusing surgery may be offered this treatment option.

\section*{Prognosis}

In clinical thyroid carcinoma, factors adversely affecting prognosis are undifferentiated carcinoma, the presence of distant metastases, lymph node involvement, local invasion, large tumors (>40 mm in greatest dimension), and greater patient age (>45 years).\textsuperscript{112,115,125,133} Prognosis of PTMC is excellent following appropriate surgical therapy and has been examined in a number of studies. Despite the high incidence of PTMC in autopsy studies (1—36%, see above) thyroid cancer accounts for only
PTMC can be lethal because small numbers of patients develop locoregional recurrences and distant metastases.\textsuperscript{7,82,141} The majority of PTMC recurrence is locoregional, in the thyroid bed and neck lymph nodes, and occurred in 0–11% of patients, mostly during the first 10 years of follow-up.\textsuperscript{7,14,35,66} In the Mayo Clinic study,\textsuperscript{7} which included 535 patients treated in a 50-year period, who were followed for 17.5 years (mean follow-up) local (thyroid bed) recurrences were unusual, but were found by 10, 20, and 30 years in 0.6%, 2.0%, and 3.6%, respectively. Although most recurrences can be cured after further neck surgery,\textsuperscript{87} recurrences may contain cancer cells showing a more aggressive phenotype. In the study by Rodriguez et al.\textsuperscript{21} two of the 3 patients with recurrence at the time of initial presentation. In a similarly large study from the Noguchi’s thyroid clinic in Japan, which included 867 patients followed for 12.8 years (mean), two patients died with recurrent thyroid cancer.\textsuperscript{142}

Factors of prognostic significance are listed at Table 2.\textsuperscript{7,13,15,31,48,49,53,55,56,60,64,108,137–139} Occurrence of papillary thyroid carcinoma, including PTMC, at an earlier age carries a better prognosis, even with relatively advanced nodal status.\textsuperscript{8,60,143} In general, in thyroid cancer tumor size is an important prognostic factor; PTMC have a more favorable prognosis than larger (>10 mm) tumors.\textsuperscript{7,87,115,142,144} In the recent study on PTMC by Pellegriti et al.\textsuperscript{56} tumors were subcategorized by size as less than 5, 5–10 and 10–15 mm; a progressively increasing frequency of signs of tumor aggressiveness (multifocality, bilaterality, extrathyroidal invasion, and lymph node involvement) with increasing tumor size at presentation was found. This was particularly evident for tumors larger than 10 mm with respect to tumors no larger than 10 mm in diameter.\textsuperscript{56} Tumor size greater than 10 mm was associated with the presence of multifocal or bilateral thyroid tumor, extrathyroidal invasion, and local lymph node metastases. However, there was no association between tumor size greater than 10 mm and the presence of distant metastases.\textsuperscript{56} Furthermore, tumor size was not a significant predictor of tumor persistence or recurrence.

The presence of lymph node metastases, according to most\textsuperscript{15,35,65,77,126,141,146} but not all\textsuperscript{147} investigators does not worsen the prognosis nor it increases mortality; in the study by Appetecchia et al.\textsuperscript{35} which included 120 patients with PTMC, despite the presence of neck metastases in 22% of patients and of local invasion beyond the thyroid capsule in 20 (17%), only 1.7% of patients developed local recurrence. More important prognostic factors for recurrence seems to be extra-thyroidal spread, recurrence in the thyroid remnant or in the thyroid bed, and distant metastases.\textsuperscript{35} However, in the Mayo Clinic study, lymph node metastases had prognostic significance regarding the risk for recurrence;\textsuperscript{7} the rate of recurrence in the node-negative group was 1%, while that in the node-positive group was 18%. Interestingly, in the same study, lymph node metastases did not affected survival.\textsuperscript{7} Similar results have been reported by other investigators.\textsuperscript{56,108} Lymph node metastases may be present even in small PTMC (minute carcinoma <5 mm, and tiny carcinoma 5–10 mm),\textsuperscript{49} but their prognostic significance remains questionable.\textsuperscript{9} Rarely, PTMC may be associated with distant metastases (see above, ’’Oncogenesis and Natural History’’), usually in association with lymph node metastases. Some of these metastases have proven fatal.\textsuperscript{7,12,48,64,142,145,147–150} Multifocality has prognostic significance. In the study by Baudin et al.\textsuperscript{87} the recurrence rate for patients with unifocal PTMC was 1.2% compared with 8.6% for patients with multifocal PTMC. In the same study, the recurrence rate following total thyroidectomy was 2.3% compared with 8.2% after unilateral lobectomy plus isthmusectomy. Other unfavorable prognostic factors that have been described for PTMC include extracapsular invasion and extracapsular invasion through the lymph node capsule,\textsuperscript{95,151} bulky lymph

### Table 2
Unfavorable prognostic factors (increased risk for recurrence) (Ref. #)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Ref.</th>
</tr>
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<tbody>
<tr>
<td>Older age (&gt;45 years)</td>
<td>48,60,139</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>48,60,139</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>31,60</td>
</tr>
<tr>
<td>Unencapsulated tumor</td>
<td>56</td>
</tr>
<tr>
<td>Multifocality</td>
<td>48,60,139</td>
</tr>
<tr>
<td>Lymph node metastases</td>
<td>56</td>
</tr>
<tr>
<td>Vascular invasion</td>
<td>56</td>
</tr>
<tr>
<td>Sclerosant variant</td>
<td>55,56</td>
</tr>
<tr>
<td>Male gender</td>
<td>56, (?)</td>
</tr>
<tr>
<td>Nonincidental cancer</td>
<td>56</td>
</tr>
<tr>
<td>Grave’s disease</td>
<td>56,108, (?)</td>
</tr>
<tr>
<td>Extend of initial surgery (total/near total thyroidectomy vs. lobectomy/isthmusectomy)</td>
<td>7</td>
</tr>
<tr>
<td>Increased postoperative thyroglobulin levels</td>
<td>50</td>
</tr>
<tr>
<td>DNA aneuploidy</td>
<td>7</td>
</tr>
</tbody>
</table>
node metastases, hoarseness caused by recurrent laryngeal nerve invasion and palsy,\textsuperscript{115} the sclerosant variant of the tumor,\textsuperscript{55,56,152} increased postoperative thyroglobulin levels,\textsuperscript{150} increased cyclin D1 overexpression, p27 underexpression, immunohistochemical expression of transforming growth factor β-3 or Ki-67,\textsuperscript{101,102,115,151} and increased expression of p53, bcl-2, c-erbB-2, and p21.\textsuperscript{153,154} In the study by Pellegriti et al.,\textsuperscript{56} male gender and Grave’s disease have been associated with a worse outcome, but this has not been a consistent finding across other studies.\textsuperscript{155} It is plausible that thyroid-stimulating Igs could promote tumor growth in Grave’s disease patients. Endemic goiter is negatively associated with relapse in the subgroup of non-incidental PTMC.\textsuperscript{56} Familial PTMC were not more aggressive or more likely to be associated with persistence or recurrences in the same study,\textsuperscript{56} a finding that differs from other reports, that suggested a more aggressive management of this subtype of PTMC.\textsuperscript{156} It is likely that familial PTMC is not a single, unified entity, and the various forms of familial PTMC may well behave differently. Of note, patients with incidentally discovered PTMC (following surgery for a presumably benign thyroid disease) had a lower (5.2%) risk for tumor persistence or recurrence than the patients with non-incidental disease (10.4%), despite the fact that surgery for the non-incidental tumors was more aggressive.\textsuperscript{56} Patients from endemic goiter regions had a decreased risk for persistent or relapsing disease, although this finding was of borderline significance, and was seen only in the non-incidental tumor group.\textsuperscript{56,108} The theoretical basis behind this clinical finding is unknown.

The combination of age, (presence of) metastases, extent, and (tumor) size (AMES) has been proposed as a prognostic scoring system to stratify PTMC patients into low and high-risk groups for prognostication.\textsuperscript{157} Other prognostic scoring systems have also been proposed.\textsuperscript{158}

**Follow-up**

The term “carcinoma” in the pathology report is usually disturbing for both the patient and the unwary surgeon and sends a message with considerable therapeutic, prognostic, psychological, and financial impact. Obviously, all these issues and in particular psychology should be taken into consideration when discussing a follow-up schedule. A significant subject is what to tell the patient when an incidental PTMC has diagnosed following surgery for a presumably benign thyroid disease. Usually, the diagnosis of “carcinoma” will have a far greater impact on the patient than the justified by the biological potential of the PTMC. Some authors suggested that “carcinoma” should not be mentioned in younger patients who have a completely excised PTMC.\textsuperscript{159} These authors note that the “benign” behavior of these tumors may not warrant the potential social and economic complications of a “cancer” diagnosis and the subsequent follow-up strategies. However, this may be an unacceptable approach for many practitioners and therefore it is an issue for the individual surgeon to decide on. In our clinical practice, we discuss with our patients the diagnosis and the exact nature of the disease, emphasizing the benign biological behavior of this neoplasm and its high curability rate and excellent prognosis. This allows the patient to accept adjuvant therapy (i.e., radiiodine therapy) and to participate to any suggested follow-up program.

Although predictors of relapse or persisting disease are quite well established in large papillary thyroid cancers, they have not been consistently identified in small papillary thyroid cancers, including PTMC (see above, Prognosis). The recognition of those PTMC that have the potential to spread/relapse and even cause patient death would be of particular clinical significance. These potentially aggressive PTMC would require close follow-up and intensive treatment, whereas the follow-up of the low-risk PTMC, which represent the large majority of PTMC, does not require costly and complex medical procedures and should be simplified.

Following total or near-total thyroidectomy, patients with PTMC should be followed by measurement of thyroglobulin (Tg) serum levels (after L-T4 withdrawal), neck ultrasonography, and whole body scan (I\textsuperscript{131}). Serum Tg levels at the first postsurgical evaluation after L-T4 withdrawal have a significant prognostic importance. Patients considered disease-free at that time, because of having a Tg serum level below 1 ng/ml, had approximately 1% probability to develop a local recurrence, and, most importantly, none of them developed distant metastases.\textsuperscript{56} In these patients, follow-up can be simplified as already suggested for low-risk differentiated thyroid cancer.\textsuperscript{160} In this group of patients, I\textsuperscript{131}-whole body scan does not add further information.\textsuperscript{56} In contrast, in patients with serum Tg of at least 1 ng/ml at first postsurgical evaluation, the probability of tumor relapse is increased (16% and 68% relapse rate for Tg levels 1–10 ng/ml and Tg levels >10 ng/ml, respectively).\textsuperscript{56} In this group of patients the risk of tumor recurrence can be accurately predicted by considering the presence or the absence of a variety of histopatholo-
gical risk factors (metastatic lymph nodes, sclero-
sant variant, bilateral foci, non-incidental cancer
and extrathyroid invasion). Patients not cured by
surgery could be identified by the combination of
serum Tg measurement plus neck ultrasonography,
making the role of $^{131}$I whole body scan question-
able. Based on these findings, it seems reason-
able to consider patients with undetectable initial
stimulated serum thyroglobulin values, without
detectable thyroglobulin antibodies, as cured.
These patients require only minimal long-term
monitoring. Patients with initial TSH-stimulated
serum thyroglobulin values greater than 10 ng/ml
probably have persistent tumor and should be fol-
lowed closely. Risk for recurrence of the inter-
mediate group can be stratified based on other
prognostic variables, with patients over age 45
years, those with lymph node involvement or extra-
thyroidal invasion, and those with non-incidentally
discovered tumor being at higher risk and requiring
more intensive monitoring.

In conclusion, PTMC is frequently diagnosed to-
day, mainly as a result of the wide use of neck
ultrasonography in the evaluation of the carotid
arteries and thyroid. PTMC should be treated by to-
tal/near total thyroidectomy, provided it can be
performed safely. We recommend adjuvant post-
operative radioactive therapy for high risk lesions.
Central lymph node dissection is indicated in the
presence of neck lymphadenopathy. Suppression
therapy is needed following surgical therapy. De-
spite the potential for neck lymph node and even
— albeit very rare — distant metastases, prognosis
of PTMC is excellent.

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Papillary thyroid microcarcinoma: A surgical perspective


