Review Article

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Managing Thyroid Microcarcinomas

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Papillary thyroid microcarcinomas (PTMCs) are the most common form of classic papillary thyroid carcinoma (PTC). PTMCs are typically discovered by fine-needle-aspiration biopsy (FNAB), usually with sensitive imaging studies, or are found during thyroid surgery in a patient without a previously known history of thyroid carcinoma. However, the definition of PTMC has not always been universally accepted, thus creating controversy concerning the diagnosis and treatment of PTMC. The aim of this review is to summarize the clinical features of PTMC and identify the widely differing opinions concerning the diagnosis and management of these small ubiquitous thyroid tumors.

Key Words: Papillary thyroid cancer, papillary thyroid micro-carcinoma, fine-needle aspiration biopsy, TNM staging systems, autopsy studies, BRAF V600E

BACKGROUND

Prior to 2003, papillary thyroid microcarcinomas (PTMC) was defined by the World Health Organization (WHO) as a tumor 1 cm or less in diameter[1] but in 2004 this definition transiently changed to a new classification requiring that PTMC tumor must also be found incidentally. At the same time, the 5th UICC (International Union Against Cancer) and AJCC (American Joint Commission on Cancer) TNM staging systems-(Tumor),- (Node)-, (Metastasis), defined PTMC as T1, a tumor 1 cm or less in greatest dimension. However, in 2002 the 6th edition of the TNM staging system[2] changed the definition of T1 to a tumor 2 cm or less in greatest diameter or limited to the thyroid, which altered both the WHO and TNM standards for PTMC to the extent that no prognostic definition for PTMC existed to predict the course of PTMC and the long-term outcome for an individual patient.[3] Much of these changes are related to the rising incidence rates of papillary thyroid cancer (PTC), particularly in the form of PTMCs <1 cm.[3]

CHANGING INCIDENCE RATES OF THYROID CANCER IN THE UNITED STATES

The incidence rates of PTC are growing at a faster rate than any other malignancy

in the USA and have been steadily rising according to the National Cancer Institute (NCI) Surveillance Epidemiology and End Results (SEER) program.[4]

Hughes, et al.[5] performed a retrospective study to evaluate the effects of age on the influence of the increasing incidence rates of PTC as reported in the NCI SEER database. From 1973 to 2006, the age group most commonly found to have PTC shifted from patients in their 30's to patients in the 40-50 year-old group. However, by 1973, 60% of patients with PTC were younger than 45, and the majority continued to be younger patients until 1999. Thereafter, PTC became more common in patients older than 45, and by 2006, 61% were older than 45 years. From 1988 to 2003, there has been an increasing incidence of PTC in all sizes and at all age groups, with the largest increase being in tumors <1 cm (PTMCs) in patients older than 45. However; 43% of tumors in patients older than 45 were <1 cm (PTMCs) and only 34% were younger than 45. Moreover, of the nearly 20,000 thyroid cancer cases in 2003, 24% were PTMCs in patients over the age of 45.[5]

Commentary

Perhaps the most important finding in this study is that the number of PTCs <1 cm (PTMCs) are increasing in all ages but is disproportionally high in patients older than 45, and the changing patterns relating age and incidence rates have important prognostic and treatment implications for patients with PTMC. Yet how age affects the incidence rates of PTMC remains uncertain, but is nonetheless consistent in most countries.

THYROID CANCER RATES IN FIVE CONTINENTS

Kilfoy, et al.[6] analyzed the trends in the incidence of thyroid cancer across five continents (C15), over a 30-year period from 1973 to 2002 and has increased in 19 populations in the Americas, Asia, Europe, and Oceania, during which there was considerable variation in the thyroid cancer incidence rates in every continent but Africa. This trend has also been found in many other countries across Europe, Asia, Oceania, and South America, with the only countries reporting a decline in thyroid cancer being Sweden (18%), Norway (5.8%), and Spain (25.9%) while there was an increase in Switzerland (5.3%) and France (155%) with the greatest increase occurring in southern Australia where the incidence rates increased 177% in men and 252% in women. The incidence rates have also increased in children and adolescents at a rate of 1.1% per year in the U.S.[7] and in England,[8] and have increased at an even greater rate of 3% per year across Europe.[9] Still, thyroid cancer remains a relatively rare tumor that represents only 2% of all cancers in the U.S.A.[10]

Commentary

Thyroid cancer incidence rates have been increasing around the world, the cause of which is multifocal but also remains partially uncertain. The rise in PTMC has sparked a wide range of controversies beginning from about 1955, and thereafter has increased significantly.[11-13]

THE RANGE OF PTMCs IN AUTOPSY STUDIES

Pazaitou-Panayiotou, et al.[13] identified 24 autopsy studies that were performed in 1986 through 2005 during which 7,663 autopsy cases of thyroid cancer were performed, and the prevalence rates of PTMC ranged from 2% to 35.6%, using tumor resection techniques ranging from 1-2 mm to 3-5 mm, with the majority making 2-3 mm tissue resections (66%). A review of several other autopsy studies[14] found that approximately one-third of adults have at least one PTMC

The authors also identified 11 surgical series of patients treated for benign thyroid disease that had incidental coexistence with PTMC. The prevalence of PTMC ranged from 1.3% to 21.6%, and the relationship between PTMC and thyrotoxicosis varied from 0.3% to 5.7%[15,16] in surgical specimens, an association that varies among surgical series,[17-19] and the risk of thyroid malignancy in multinodular goiter was comparable to that of solitary thyroid nodules.

Commentary

Autopsy studies have played a key role in clinical decision-making in patients with PTMCs.

AUTOPSY STUDIES FROM THE USA ARMED FORCES INSTITUTE OF PATHOLOGY (AFIP)

Silliphant, et al.[20] performed one of the largest and earliest analyses of autopsy studies in 1944 through 1958 from the AFIP among the more than 240,000 autopsy reports in

Washington, DTC,[20] among which 117 autopsy protocols of persons dying without suspicion of thyroid disease revealed that only 45 (38%) of the protocols contained any reference to the thyroid gland. It was the authors' opinion that the number of thyroid cancers found at autopsy is dependent on the zeal of the prosector in searching for thyroid cancer. The validity of this idea was supported by the 1955 work of Mortensen, et al.[21] in which a painstaking search for thyroid cancer at autopsy found 28 primary cancers of the thyroid gland in 1,000 routine consecutive autopsies, and only 2 of the 28 cancers were recognized on a routine postmortem examination. When the same thyroid glands were examined more carefully, all grossly recognized nodules were studied histologically, and 26 additional occult thyroid cancers were discovered, comprising an incidence rate of 2.8% in the 1,000 consecutive routine necropsies.

Commentary

Autopsy studies have generated considerable controversy regarding the diagnosis and treatment of PTC and PTMC based upon the prevalence of these tumors in autopsy studies as a guide to forgo *in vivo* therapy for patients with PTC or PTMC, which is directly related to the rising incidence rates of thyroid cancer.

STUDIES EVALUATING THE RISING INCIDENCE OF PTC AND PTMC THYROID CANCER

Davies and Welch,[22] performed a retrospective study in 2006 that examined the trends in thyroid cancer incidence, histology, tumor size and mortality. The study was performed on data in the NCI SEER program on thyroid cancer. The main finding was that the incidence of thyroid cancer increased from 3.6 per 100,000 in 1973 to 8.7 per 100,000-a 2.4-fold increase-[95% confidence interval (CI): 2.2-2.6]; $p<0.001$ for trend. There was no significant change in follicular, medullary, and anaplastic cancer ($p>0.20$ for trend). The most important observation was that virtually the entire increase in thyroid cancer was the result of an increased incidence of PTC that advanced from 2.7 to 7.7 per 1,000,000, which is a 2.9-fold increase (95%CI: 2.6-3.2: $p<0.001$ for trend). Moreover, between 1988 and 2002, 49% of the increase rates (95% CI: 47-51%) were from PTMCs <1 cm; and 87% (95% CI: 85-89%) were from thyroid cancers <2 cm. Thyroid cancer mortality was stable between 1973 through 2002 at approximately 0.5 deaths per 1,000,000. The authors concluded that the increasing incidence of thyroid cancer in the USA is predominantly due to the increased detection of PTMCs, which the authors attribute to the "known existence of a substantial reservoir of subclinical cancer" and stable overall thyroid cancer mortality, suggesting to the authors that the increasing incidence of thyroid cancer reflects an enhanced detection of subclinical disease, not an increase in the true occurrence of thyroid cancer. The authors expressed the opinion that further studies will be needed to determine if a more cautious diagnostic approach is worthwhile and perhaps simply providing follow-up for symptomatic thyroid nodules may be worthwhile, and thyroid cancers <1 cm could be classified as a normal finding. The authors identified a study by Vanderlann[23] as a 50-year old study that pathologists reported thyroid cancer-especially -PTC- was a common autopsy finding, despite the fact that the patients never had symptoms during lifetime.

Commentary

A study conducted in Ontario, Canada by Kent, et al.[24] reported a similar increase of differentiated thyroid cancers ≤1 cm to 2 cm in diameter. Nonetheless, it is not likely that many patients would agree that a small thyroid cancer is a "normal phenomenon", especially since we do not always know the growth rate of a patient's PTMC without careful study and long term follow-up evaluation. Also, there are studies that challenge the concepts reported by Davies and Welch.

Enewold, et al.[25] performed an analysis aimed at further understanding the rising thyroid cancer incidence rates that have been attributed to heightened medical surveillance and the use of improved diagnostic tests. The authors hypothesized that if the increased incidence of thyroid cancer was entirely due to improved disease detection, then one would expect a greater number of small early-stage tumors, which in turn should decrease the incidence rates of large tumors of other histologies except for anaplastic cancer. Thyroid cancer incidence rates vary by sex and race/ethnicity, and these factors influence access to and utilization of healthcare. The authors thus examined thyroid cancer incidence rates by studying demographic and tumor characteristics of 48,403 patients with thyroid cancer diagnosed during 1980-2005 from the NCI SEER program. The incidence rates varied by the type of histology, sex, and race/ethnicity, and PTCs were the only histologic type for which incidence rates increased consistently among all racial/ethnic groups.

Further analyses focused on 39,706 PTCs diagnosed during the period in which PTC rates increased most rapidly among women. Between 1992-1995 and 2003-2005, the PTC incidence rates increased nearly 100% among White non-Hispanics and Black females but increased only 20% to 50% among White Hispanics, Asian/Pacific Islanders, and Black males. The increases were most rapid for localized tumor stage and small tumors. Still, the incidence rates also increased for large tumors, regional tumors and distant stage. Since 1992-1995, half the overall increase in PTC rates was due to increasing rates of very small tumors (≤1 cm), i.e., PTMCs, and 30% to cancers 1.1 to 2 cm, and 20% to cancers >2 cm, and among White women, the incidence rate for cancers >5 cm almost equaled that of the smallest cancers.

Commentary

The main findings in this study is the conclusion that medical surveillance and more sensitive diagnostic procedures cannot completely explain the observed increases in PTMC rates, and other possible explanations should be explored. Others have reached similar conclusions.

Chen, et al.[26] performed a somewhat similar study with the goal of investigating the trends in the increasing incidence of PTMC and follicular thyroid cancer (FTC) by tumor size, age, race, and sex of differentiated thyroid cancer from 1988-2005 using the NCI SEER database. Trends in the incidence rates of PTC and FTC, race, age, sex, and primary tumor size <1.0 cm, and 1.0-2.9 cm, 3.0-3.9 cm, and >4 cm, and SEER-stage localized, regional, and distant tumors were analyzed using joinpoint regression, which was reported as the annual percentage change (APC).

The main findings were that incidence rates increased for tumors of all sizes. Among men and women of all ages, the highest rate of primary tumors was <1.0 cm (PTMC) among men in (1997-2005: APC, 9.9%) and women (1988-2005: APC, 8.6%). Significant increases also were observed for tumors >4 cm among men (1988-2005: APC, 3.7%) and women (1988-2005: APC, 5.70%) and for distant SEER stage disease among men (APC, 3.7%) and women (APC, 3.6%). The incidence rates of differentiated thyroid cancers of all sizes increased between 1988 and 2005 in both men and women.

Commentary

Enewold, et al.[25] and Chen, et al.[26] thus concluded that increased incidence rates of all tumor sizes suggests that increased diagnostic scrutiny is not the sole explanation for the high incidence of thyroid cancer, and other explanations including environmental influences and molecular pathways should be investigated.

OBSERVATION WITHOUT THERAPY FOR PATIENTS WITH PTMC ≤1 CM

Ito, et al.[27] hold the view that it is debatable whether patients with PTMC ≤1 cm should always undergo surgery, an opinion of the authors' that is related to the high incidence of occult PTCs that have been observed in autopsy studies. The authors accordingly proposed observation without surgery as a treatment option for 732 patients, 162 of which (22%) opted for observation, while 570 others (78%) opted for immediate surgery. During follow-up of the observation group, 70% of tumors either did not change or decreased to their initial size. PTMCs enlarged by more than 10 mm in 10.2%, and lymph-node metastases were found in the lateral compartment in 1.2% of patients.

Ito and Miyauchi[28] found in a 5-year follow-up study that 6.7% of PTMCs enlarged 3.0 mm or more and lymph-node metastases were detectable in 1.7% of the patients. The authors' opinion was that observation without surgery could be an attractive alternative for patients with low-risk PTMC, but occult PTMC with lymph-node metastases or distant metastases show a worse prognosis, even in incidentally detected PTMCs.

Commentary

This study has a relative short-term follow-up and observation-group patients who developed tumors were switched to the surgery group. Also, the authors acknowledge that patients with PTMC may have aggressive disease requiring more intensive treatment.

Noguchi, et al.[29] performed a study of 2,070 patients with PTMC, which found that PTMCs larger than 6-10 mm recurred in 14% of the patients after 35 years of follow-up, as compared with 3.3% in patients with smaller tumors. Patients older than 55 years had a 40% recurrence rate during a 30 year follow-up, which is a worse prognosis than that of younger patients who have recurrence rates of less than 10%. Also, extracapsular primary tumor invasion had a higher re-

currence rate, the majority of which were in the neck. During the interval between primary surgery and the first recurrence, there was 1 patient with lung metastases and 4 with bone metastases and at the interval between the primary surgery and the second recurrence, 4 more patients had lung metastases, and 1 other had bone metastases and another had a mediastinal tumor recurrence. Noguchi concluded that PTMC is similar to larger PTCs with tumor characteristics and an age-based recurrence rate that extends over many years, justifying long surveillance with ultrasonography after surgery. Also, there were significantly more metastases in the Noguchi study as that observed in the Ito study.

Commentary

Noguchi had a substantially larger study cohort with a much longer follow-up than that in the Ito study, accounting for the major differences in outcome in the two studies. The Noguchi study underscores the extent of follow-up that is necessary in patients with PTMC, especially in patients who have had surgery alone, particularly if the patient has had lymph-node metastases, tumor extracapsular invasion or distant metastases.

DIAGNOSTIC EFFECTS OF ^{18}FDG-PET IN THE ANALYSIS OF PTMC

In 2001, Cohen, et al.[30] was one of the first to identify thyroid incidentalomas by showing that these small thyroid tumors often exhibit increased metabolic activity demonstrated by glucose uptake of ^{18}Fluorodeoxyd-glucoseof^{18}FDG-PET scans with positron emission tomography (PET) and computed tomography (CT). This retrospective study reviewed all patients who had ^{18}FDG-PET imaging from June 1, 1996, through March 15, 2001 and identified patients with newly diagnosed thyroid tumors. Thyroid incidentaloma was defined as a thyroid tumor initially seen on ^{18}FDG-PET in a patient without a history of thyroid disease. A total of 102 of 4,525 ^{18}FDG-PET studies (2.3%) demonstrated thyroid incidentalomas, and 85% (87of 102 patients) had no thyroid histology because of other malignancies, but 15 patients had a thyroid biopsy, 7 (47%) with thyroid cancer, and 6 (40%) had nodular hyperplasia, 1 had thyroiditis and 1 had atypical cells of indeterminate origin. The average ^{18}FDG-PET standardized uptake values (SUVs) were higher for malignant tumors than for benign lesions which occurred at a frequency of 2.3%. Among the thyroid incidentalomas that were biopsied, 47% were found to be malignant. The author concluded that given the risk of malignancy, patients with new thyroid lesions on a PET scan should have a tissue diagnosis if it will influence outcome and management.

Commentary

Others have since confirmed the Cohen observations, and nowadays[31-34] ^{18}FDG-PET/CT scans are utilized for a variety of reasons including screening for tumors, and are found by serendipity in the evaluation of benign thyroid tumors and to perform accurate follow-up or to identify recurrent or persistent tumors. In other cases such as screening, there is concern regarding efficacy of this practice, and others suggest studies should be performed to produce positive and negative predictive values. Although PTMC is widely described as an indolent tumor, it may be associated with lymph-node metastases at the time of presentation,[32] or with locoregional recurrences during follow-up, and distant metastases occur in extremely rare cases.[32-34] All of which may be identified by^{18}FDG-PET/CT.

COMPARISON OF PROGNOSIS IN THYROID CANCERS 11-20 MM VERSUS ≤10 MM

Rossi, et al.[35] performed this retrospective study with the aim of comparing the characteristics and outcomes of differentiated thyroid cancers ≤10 cm and those with 11-20 mm diameter. The study cohort, which was treated at the University of Ferrara Clinic in Italy, comprises 243 patients with tumors ≤1 cm that was PTMC and 183 were tumors 11-20 mm that was almost exclusively PTCs that were studied. Mean patient age was >45 years in 69% and 69.9% in the PTMC and PTC groups, respectively (p=0.083), all of whom had total or near-total thyroidectomy. In addition, ^{131}I remnant ablation was administered to 96% and 94.5% of the 2 groups, respectively (p=0.226). Bilateral/multifocal tumor was 32% and 30%, respectively (p=0.366). Intracapsular tumor extension (T1 stage) was 83% and 69.4%, respectively (p=0.001). Extracapsular tumor extension (T3) at diagnosis was 17% and 30.6% respectively (p=0.001); and lymph-node-metastases at diagnosis were 13% and 25.1%, respectively (p=0.001); and distant metastases at diagnosis were 1.6% and 3.8%, respectively (p=0.095). However, there are problems with the 5th edition TNM stage as compared with the 6th edition TNM stage.

With the 5th TNM edition, 48 patients (26.22%) were stage I, but with the 6th edition, there were 125 Stage I patients (p<0.001); with the 5th edition, 47 patients (25.68%) were stage II, and with the 6th edition there were 4 Stage II patients (p<0.001); With the 5th edition, 85 patients (46.44%) were stage III, and with the 6th edition there were 50 (27.32%) stage III patients, (p<0.001). With the 5th edition, 3 patients (163%) were stage IV, and with the 6th edition there 4 (2.18%) stage IV patients (p<0.276).

By multivariate analysis, the presence of lymph node metastases correlated with the diameter of the tumor (p<0.004): patients with cancer 11-20 mm in diameter had a 2.1-fold higher probability of having lymph-node metastases at the time of diagnosis. Also, capsular invasion significantly predicted lymph-node metastases at diagnosis: patients with capsular invasion had a 1.9-fold higher probability of having lymph-node invasion at the time of diagnosis, and women had a threefold lower probability of having neck lymph-node metastases at the time of diagnosis as compared with men (p<0.001).

The prevalence of distant metastases thus did not differ between PTMCs ≤1 cm and 11-20 mm cancers. Also 133 patients (73%) with cancers 11-20 mm were disease-free 2 years after ^{131}I therapy, and no recurrence was observed over 2-14 years of follow-up. However, 41 patients (22%) with cancers 11-20 mm (N1 or M1) required 2-4 years to become disease-free. Neck lymph-node recurrence was observed in nine patients (4.9%) 4 months to 14 years after surgery and ^{131}I therapy. Four patients (1.6%) with cancers ≤1 cm and 10 in diameter had cancer recurrence (p=0.05 compared with the 11-20 mm cancers). The authors concluded that the presence of distant metastases at diagnosis and recurrence of disease during follow-up, cancers 11-20 mm in diameter seemed more aggressive than cancers ≤1 cm (p<0.05) and cancers 11-20 mm seem more aggressive than those ≤1 cm than >10 cm.

Commentary

This study suggests that PTMC and tumors 11-20 mm that have lymph-node metastases, tumor invasion, or extracapsular extension or with distant metastases should provoke considerable evaluation and appropriate therapy.

SIZE ALONE DOES NOT GUARANTEE LOW RISK IN INCIDENTALOMAS

Nam-Goong, et al.[36] performed a retrospective study of ultrasound-guided FNAB (US-FNAB) aimed at defining the rate of malignancy in patients with incidentally detected impalpable thyroid nodules and to evaluate the extent of disease in patients with cytology results suspicious of malignancy using US-FNAB. The authors identified the records of 267 patients who were studied from January 2000 to December 2001 who had a total of 317 impalpable nodules. The average nodule size was 0.9±0.3 cm, (range 0.2 cm to 1.5 cm), all of which were impalpable. A total of 101 (32%) US-FNAB cytology specimens were inadequate,139 (44%) were benign, 29 (9%) were indeterminant, and 4 (1%) were suspicious for follicular or Hürthle cell neoplasm, and 42 (13%) were suspicious or consistent with PTCs, and 2 others had tumors measuring <0.5 cm, 22 with 0.5-1.0 cm i.e., PTMCs in most cases and 18 with 1-1.5 cm i.e., PTC in most cases. However, nodule size was not related to the probability of obtaining an adequate specimen for a cytology diagnosis. Forty of 48 patients with suspicious or malignant cytology had surgery, and the cytological diagnosis of PTC was histologically confirmed in all 35 patients. One of 3 patients with a cytological diagnosis of follicular neoplasm had follicular cancer. Extrathyroidal tumor extension was observed in 36 patients with well-differentiated thyroid cancer; extrathyroidal extension was observed in 16 of 36 patients (44%), and regional lymph node metastases were found in 16 of 36 patients (50%), and multifocal tumors were identified in 14 of 36 patients (39%). The rate of malignancy in incidentally detected impalpable thyroid nodules was 12% in a retrospective analysis in this group of patients. Among this subgroup, 25 of 36 (69%) patients either had extrathyroidal extension or regional lymph-node metastases and 14 of 36 (39%) had multifocal tumors at surgery, suggesting that small tumor size alone does not assure low risk in incidentally identified thyroid cancers. The authors concluded that US-FNAB is a useful diagnostic method in patients with impalpable thyroid nodules.

Commentary

This is one of the earlier studies that document the diagnostic efficacy of ultrasound-guided-guided FNAB in PTMCs.[37] The main finding was that a substantial number of patients either had extrathyroidal extension or regional lymph-node metastases, indicating that small tumor size alone does not guarantee low risk in incidentally identified thyroid cancer evaluated with US-guided FNAB, which is consistent with other studies[38-41] that suggest PTMC can sometimes be an aggressive tumor.

THE IMPACT OF TUMOR SIZE AND OUTCOME OF PTMC

Bilimoria, et al.[40] performed a retrospective study of the American College of Surgeons National Cancer Data Base (1985-1998) with the object of retrospectively examining 52,173 patients with PTC to determine whether the extent of surgery affects the outcomes for PTC and whether tumor size thresholds exist for recurrence and mortality for PTC. The study found that total thyroidectomy results in lower recurrence and improved survival rates for PTCs ≥1.0 cm as compared with lobectomy.

The specific outcomes were as follows: Ten-year tumor recurrence rates were 4.6% with tumors <1 cm, i.e., PTMCs, 7.1% for tumors 1-1.9 cm, (1 cm or less=PTMC), and 8.6% for tumors 20-2.9 cm, (PTCs) 11.6% for tumors 30-3.9 cm, 17.2% for tumors 4.0-8.0 cm and 24.8% for PTC tumors >8 cm. The 10-year cancer-specific mortality rates were significantly increased (p=0.040) only for tumors larger than 4.0 cm. Of the nearly 6,000 patients with tumors ranging from 1-2 cm, (PTC) those treated with lobectomy experienced a 24% higher risk of recurrence and 49% had a higher risk of cancer death as compared with those treated with total thyroidectomy. Lastly, for patients with tumors ≤1 cm (PTMC), those treated with lobectomy experienced a 15% higher risk of recurrence and a 31% higher risk of cancer death (p=0.04) as compared with larger tumors.

Commentary

This study demonstrates that PTC tumors ranging from 1-2 cm in diameter may have a more aggressive behavior than has been readily apparent in studies of PTC tumors ≤1 cm alone.

THE DIFFERENCE BETWEEN NONINCIDENTAL AND INCIDENTAL PTMC

Lin, et al.[41] performed a retrospective study designed to test the hypothesis that less aggressive surgical treatment such as lobectomy or subtotal thyroidectomy is adequate therapy for incidental PTMC and whether total thyroidectomy followed by ^{131}I remnant ablation is effective for nonincidental PTMC. The study also investigated the clinical manifestations of incidental and nonincidental PTMC. The study subjects were selected from a total of 1,676 patients with PTC who had surgery and follow-up from 1977 to 2006 at Chang Gung Medical Center in Taiwan. Among this large group of patients, 335 (20%) had PTMC defined as papillary cancer ≤1 cm. All patients with PTMC were stratified as incidental (group I) or nonincidental (group II), and 209 group II patients were further categorized as intrathyroidal tumor (group IIA), or neck lymph node metastases or local regional soft-tissue invasion (group IIB) or distant metastases (group IIC). Frozen sections obtained during surgery were evaluated to select the most significant nodules, and to identify the most invasive tumors in order to plan surgical dissection of the tumor.

The main findings were that in group I, 105 of 126 (83%) patients received only subtotal thyroidectomy or lobectomy, and none died of thyroid cancer. The evaluation of histology revealed 12 patients with multicentric PTMC (9.5%) in group I and 52 (24.9%) in group II (p<0.05) in the two groups respectively. In group II, 55 of the 209 patients (26.3%) were found to have extrathyroidal tumor involvement. Two patients in group I had a relapse, and 20 in group II had a relapse by the end of follow-up. One patient in group IIB with local regional soft-tissue invasion and two in group IIC with distant metastases died of thyroid cancer, and nine out of ten patients in group IIC had a diagnosis of distant metastases before primary thyroid surgical treatment. The authors concluded that subtotal thyroidectomy is effective surgical treatment for incidental PTMC, whereas nonincidental tumors require aggressive treatment that is essential for reducing the risk of cancer relapse or mortality.

Commentary

The authors make a strong case that patients with PTMC generally have an excellent prognosis and do not require adjuvant ^{131}I therapy, whereas aggressive surgery and postoperative ^{131}I adjuvant therapy is indicated for patients with nonincidental PTMC with distant metastases or regional tumor invasion or lymph-node metastases.

PREDICTORS OF TUMOR RELAPSE AND FACTORS INFLUENCING DECISIONS TO TREAT PTMC

Pellegriti, et al.[42] performed a retrospective study aimed at identifying predictors of tumor relapse in small PTCs treated at the University Catanzaro, Italy between 1975 and 2001.

The study group comprised 299 patients who had surgery for PTC ≤1.5 cm. Near-total or total thyroidectomy was performed in 292 patients with PTC no larger than 1.5 cm and lobectomy was performed on seven patients. Persistent/recurrent disease was found in 77 patients, and in 37 of these patients, the only sign of persistent tumor was an increased TSH-stimulated serum thyroglobulin (Tg). Ten patients had distant metastases, and 68 had locoregional metastases. All 284 patients who had near-total or total thyroidectomy were examined after levothyroxine (LT_4) withdrawal. Patients with low residual ^{131}I neck uptake, (<3%) and with tumors at low risk according to TNM staging, neck ultrasonography and whole-body ^{131}I scan were performed after 5 mCi (185 MBq) ^{131}I, and in 43 patients with residual cervical ^{131}I uptake (>3%) were treated with 30 mCi (1,110 MBq). Lastly, 91 patients with TNM T4 and/or N1 tumor (5th edition of TNM) had postsurgical treatment with 100 mCi of ^{131}I (3,700 MBq). Residual or metastatic tumor due to recurrent disease for at least 12 months after the first postsurgical evaluation, or due to persistent disease when a ^{131}I whole-body scan was positive with or without detectable serum Tg levels. Serum Tg <1 ng/mL at the first postsurgical evaluation during LT_4 withdrawal was an accurate predictor of absence of relapse.

The authors concluded that approximately one of four patients (25%) with PTC ≤1.5 cm develops relapsing/persisting disease after surgery. Lastly, baseline histopathological tumor characteristics and serum Tg levels off LT_4 at first postsurgical evaluation accurately predicted the risk of tumor relapse. One third of tumors were multifocal and nearly one fifth were bilateral. Extrathyroidal invasion was frequent (20%) and 30.1% had locoregional metastases. Nine tumors were sclerosing variant of PTCs, and one was tall cell variant, and all the others were classic PTC. Distant metastases were present in only 8 patients (2.7%). Tumor ≤1.0 cm vs. 1.1-15 cm was not predictive of relapse, and no patient died of thyroid cancer, but 14.4% had evidence of disease at their last follow-up. Although larger cancers (1.1-1.5 cm) had a higher prevalence of signs of aggressiveness at presentation, there was no significant difference in the outcome in PTMCs <1.0 cm.

Multivariate analysis indicated that metastatic lymph-node metastases at thyroidectomy are the most important predictors of persistent/recurrent disease, and was associated with nonincidental thyroid cancer, lymph-node metastases at presentation, and bilateral tumor. The development of distant metastases was associated with sclerosing variant PTC and the presence of lymph-node metastases.

Commentary

This study does not address whether near-total thyroidectomy or lobectomy should be performed to treat patients with small PTCs, although there were signs of tumor aggressiveness including multifocality (30%), lymph-node metastases (-30%), vascular invasion (4.7%) and distant metastases (2.7%), and 25.7% had persisting/relapsing disease, suggesting that total thyroidectomy is warranted in this group of patients.

USING CLINICAL CRITERIA TO IDENTIFY PATIENTS WITH PTMC

Durante, et al.[43] performed a retrospective study at the University of Roma, Italy that attempted to define the optimal strategy for the management and long-term surveillance of very-low risk PTMC. The authors tested the hypothesis that clinical criteria could be used to identify patients with PTMC ≤1 cm with very-low mortality or low risk of recurrence. Most PTMCs ≤1 cm diameter are indolent low-risk tumors, but some behave more aggressively. As a consequence, controversies have erupted over the optimal postoperative surveillance of patients with PTMC. The authors retrospectively analyzed data from 312 consecutively diagnosed PTMCs in patients with T1N0M0 stage disease, with no family history of thyroid cancer, no history of head and neck irradiation, unifocal PTMC without extracapsular involvement, and classic PTC histology. Additional inclusion criteria were complete follow-up data from surgery to at least 5 years after diagnosis. All 312 patients had been treated with near-total thyroidectomy and (44%) had ^{131}I remnant ablation, and all had a yearly follow-up with cervical ultrasonography and serum thyroglobulin, TSH, and antithyroglobulin assays. During follow-up for 5-23 years, (median 6.7 yr), there were no deaths due to thyroid cancer or reoperations. In the first 6-12 months after surgery and last postoperative cervical sonograms were negative in all cases. Final serum thyroglobulin levels were undetectable (<1 ng/mL) and all patients treated with ^{131}I and almost all (93%) of non-RAI patients. In this study, the yearly ultrasound examinations were consistently negative even in the 76 patients (24.3%) that had follow-up for more than 10 years. The authors concluded that in the vast majority (about 75%) of all patients with PTMC, effective postoper-

ative surveillance can be based exclusively on cervical ultrasound. The authors concluded that accurate risk stratification can allow safe follow-up of most patients with PTMC with a less intensive, more cost-effective protocol. Cervical ultrasonography is the mainstay of this protocol, and negative findings at the first postoperative examination are highly predictive of positive outcomes.

Commentary

This is a carefully articulated protocol that can be used over an extensive time for as long as 10 years in some patients with PTMC; however whether such prolonged follow-up is necessary remains uncertain.

THE GUSTAVE-ROUSSY INSTITUTE EXPERIENCE WITH PTMC

Baudin, et al.[44] performed this retrospective study of PTMC with the aim of investigating the independent factors associated with tumor recurrence in an effort to define therapeutic guidelines for the management of PTMC. The study subjects were 281 patients, 207 women and 74 men, with differentiated thyroid cancer ≤1 cm who had treatment and follow-up at the Gustave-Roussy Institute in Paris.[45] The mean±SD, age at initial surgery was 41.9±13.8 years, range 6-75, and the mean duration of follow-up was 7.3±6.2 years, range 0.6-33.7 years. The latest outpatient visits occurred from 1995 for 64% and from 1991 for 90% of the patients. Eleven patients died of causes other than thyroid cancer by the end of the study. When lobectomy had been performed and PTMC was diagnosed after a histologic examination, thyroidectomy with or without neck lymph node dissection and ^{131}I therapy were considered for each case, according to prognostic factors from this group was taken into account.[45] The main conclusion of the study was that the recurrence rate for PTMC was low (3.9%), and in the authors' view, loboisthmusectomy is the treatment of choice for patients with PTMC when only one focus of cancer is found histologically, and total thyroidectomy is the optimal treatment for patients with multiple foci. Multivariate analysis found only two parameters that significantly influenced PTMC recurrence: the number of PTMC foci on pathologic examination (p<0.002) and the extent of initial thyroid surgery (p<0.01).

Commentary

This is one of the early studies that fully address the initial diagnosis and management of PTMC. The authors concluded that the recurrence rate for PTMC is low, in the range of 3.9%, and in the authors' view loboisthmusectomy is the treatment of choice for patients with PTMC when only one focus of cancer is found by a histologic diagnosis, and total thyroidectomy is the optimal treatment for patients with multiple foci, and ^{131}I therapy was considered for each patient, according to prognostic factors that were taken into account in a well-articulated approach to PTMC.

PTMC CAN BE AN AGGRESSIVE TUMOR REQUIRING MANAGEMENT SIMILAR TO PTC

Page, et al.[46] performed a retrospective 8-year study (1998-2006) with the aim of highlighting the fact that PTMC can be an aggressive tumor requiring therapeutic management similar to that of other differentiated thyroid cancers. The study subjects were 187 surgical patients managed in Head and Neck surgery at the University Hospital of Amiens France. PTMC was found in 65 patients, 52 women and 10 men mean of age 44.3 years (range 22-77 years). A total of 41 PTMCs were considered to be aggressive tumors because of the presence of risk factors such as a tumor >5 mm, multifocal PTMCs, capsular tumor invasion, vascular embolus, tumor extending beyond the thyroid capsule, and metastatic lymph-node metastases. All patients with aggressive PTMC were treated with total thyroidectomy and ^{131}I. Most of the unilateral lobectomies were primary or secondary total lobectomies as a function of the histology examination, and patients with aggressive PTMC were treated with total thyroidectomy and ^{131}I. In addition, ipsilateral recurrent laryngeal and lateral cervical lymph-node dissections were performed in 10 patients, and ipsilateral cervical lymph-node dissection was performed in 6 patients and bilateral recurrent laryngeal and lateral cervical lymph-node dissections were performed in 3 patients. No recurrence or metastases were observed after a multidisciplinary follow-up ranging from 6 months to 8 years. The main findings were that PTMC was found in 62 patients, comprising 33 (16%) of all thyroid cancers. Unilateral nodules were found in 23 patients, 1 nodule was found in 19, cases, 2 nodules in 4 cases, and 3 bilateral nodules were found in 2 cases. Multinodular goiter was found in 32 patients, and Graves' disease goiter was found in 5 patients. A total of 11 FNABs were performed; 8 were positive (malignant tumors) and 3 were neg-

ative. In the 8 positive cases (12.9%), the existence of cancer was suspected before surgery, and in the other patients, the microcarcinomas were found coincidentally. A total of 41 of 62 patients (66.13%) of all PTMCs were considered to have aggressive tumors. There were 65 patients in the group with PTMC ≤1 cm that was considered to be aggressive because of several risk factors such as tumor >5 mm, multifocal PTMCs, tumor capsular invasion, vascular embolus, tumor extension beyond the thyroid capsule and lymph-node metastases. Of the 62 patients, 25 (40.32%) had PTMC, 15 had multifocal tumors (24.19%), respectively, 24 had thyroid capsular invasion (38.71%), 13 had lymph-node metastases (20.97%), respectively and 3 had vascular embolus (4.84%); however, the most frequent risk factors were thyroid capsular invasion and tumors with the largest diameter >5 mm.

The authors concluded that total thyroidectomy is the surgical treatment of choice for the management of PTMCs, although no consensus has been reached concerning lymph-node surgery, and it appears to be performed only in the presence of lymphadenopathy on medical imaging or is detected during surgery.

Commentary

This is a long-term study in which the authors have achieved their goal of highlighting the fact that PTMC can be an aggressive tumor requiring therapeutic management similar to that of other differentiated thyroid cancers. Several other studies have found that PTMC >5 mm, thyroid capsular invasion, vascular emboli, tumor extending beyond the thyroid capsule, lymphadenopathy, and organ metastases may occur with PTMC.[44-49]

BRAF^{V600E} AND THE CLINICAL, PATHOLOGICAL, AND PROGNOSTIC FEATURES OF PTMC AND OVERT PTC

Basolo, et al.[48] performed this study with the aim of retrospectively correlating *BRAF*^{V600E} mutation with different clinical and pathological features in a large homogeneous series of PTCs 20 mm or smaller, and in addition, the authors also investigated the relationship between *BRAF*^{V600E} and the degree of neoplastic infiltration of PTCs smaller than 20 mm to redefine the reliability of the risk stratification system for PTCs smaller than 20 mm.

As the degree of neoplastic infiltration beyond the thyroid capsule remains an exceptional parameter that can be evaluated by histopathological examination of a PTC 20 mm or less in size as a pT1 or pT3 tumor. The authors correlated a *BRAF*^{V600E} mutation with both clinical and pathological features and the degree of neoplastic infiltration to redefine the reliability of the current system of risk stratification in a large selected group of PTCs smaller than 20 mm. The presence of BRAF mutations was examined in 1,060 PTCs less than 20 mm divided into four types of neoplastic infiltration: 1) totally encapsulated; 2) not encapsulated without thyroid capsule invasion; 3) thyroid capsule invasion; and 4) extrathyroidal extension.

The main results were that the overall frequency of the *BRAF*^{V600E} mutation was 44.6%. Both univariate and multivariate analyses demonstrated that *BRAF*^{V600E} mutations had a strong association with PTC variants such as classical PTC and tall cell variant, thyroid cancer size 11-20 mm, tumor multifocality and absence of tumor capsule, extrathyroidal extension, lymph node metastasis, higher AJCC cancer stage, and younger patient age. In PTCs staged as pT1 with thyroid capsule invasion, *BRAF*^{V600E} mutation was significantly higher than in pT1 tumors that did not invade the thyroid capsule (67.3% vs. 31.8%, respectively), $p<0.0001$. There was no statistically significant difference in *BRAF*^{V600E} alterations between pT1 tumors with thyroid capsule invasion and pT3 tumors, 67.3 and 67.5%, respectively.

The authors concluded that evaluation o f *BRAF*^{V600E} status would be useful even in pT1 tumors to improve risk stratification and patient management, and PTCs <12 mm limited to the thyroid (pT1) are low-risk tumors, which in the absence of lymph-node metastases can be successfully treated with total thyroidectomy alone; however PTCs of the same size with extrathyroidal extension (pT3) have a higher likelihood of metastases and persistent/recurrence that requires more aggressive treatment.

Commentary

The correlation between patient age and *BRAF*^{V600E} mutation has been the subject of considerable controversy.[37-39,50-56]

Lee, et al.[55] performed this study as a result of the conflicting data on the usefulness of *BRAF*^{V600E} and as a consequence performed a meta-analysis of *BRAF*^{V600E} that included 12 studies with a total of 1,168 patients in which the frequency of *BRAF*^{V600E} mutation was 49%. The *BRAF*^{V600E} mutation was found to be associated with PTC histologic subtype, the presence of extrathyroidal extension and high-

er clinical stage, but was not associated with age, sex, race, or tumor size, but the authors concluded that effect of the *BRAF*^{V600E} mutation on the poor prognosis of PTC was apparent in the meta-analysis, and the authors concluded that their study confirms the status of *BRAF*^{V600E} that may be used as an important prognostic marker of patients with PTC and may be useful even in pT1 tumors that are important prognostic markers of patients with PTC.[55-58]

Park, et al.[57] performed this retrospective study with the aim of assessing the high recurrence rates of PTMC ≤1 cm in what is typically considered to have a benign course during a patients' lifetime, thus prompting the authors to perform this retrospective study at Seoul National University Hospital, Seoul, Korea, aimed at analyzing the clinicopathological features, long-term prognosis, and molecular characteristics of *BRAF*^{V600E} mutation. The study subjects were 175 men and 975 women, mean age 45.6±13.3 years that had total thyroidectomy for PTC between 1983 and 2004. The study comprised 1,150 patients with PTC, 868 with PTC >1 cm and 279 with PTMC ≤1 cm, which is generally regarded as an incidental finding that is present in up to 30% or 40% of surgical or autopsy cases.[60-64]

Although PTMC ≤1 cm is generally considered to have a lifetime course, studies now report recurrence rates up to 20%,[31,32,35,43] and several cases of distant metastases with fatal outcome have been described in patients with PTMC.[64-71] However, there are significant differences in the demographic and pathologic findings and prognosis between incidental PTMCs and those found incidentally at autopsy which are found in up to 30 to 40% of autopsy studies.[49,50,54] PTMCs diagnosed by imaging studies[68] include small PTCs that might represent an early phase in the development of overt PTCs >1 cm. Still, only a few studies have reported the clinicopathologic characteristics of PTMCs.[70-76]

The authors of this study point out there is a particularly high frequency of activating mutations in the *BRAF* kinase gene *BRAF*(^{V600E}) mutation in patients with PTC, which was described in Koreans.[70] The *BRAF*(^{V600E}) mutation was found to be associated with old age, male sex, lymph-node metastases, and multifocal tumors.[71] The authors were motivated to further study the characteristics of PTMCs by analyzing the *BRAF*^{V600E} mutation, and the pathological findings and clinical outcomes between patients with PTMC and PTC to further investigate the clinical significance of recently detected PTMCs. Also investigated were the expression of molecular markers associated with PTC that compared the molecular characteristics of PTMC and overt PTC.

The major results were as follows: the prevalence of extrathyroidal invasion (52.2%) and initial nodal metastasis (34.9%) in patients with PTMC was unexpectedly high and almost as high as that for patients with PTC (72.4% and 51.8%, respectively). The rate of recurrent or persistent disease did not differ between patients with PTMC and PTC. The rate of recurrent or persistent disease, was 6.1% vs. 14.1%; 53.4 vs. 84.2-month follow-up n=98 vs. 647; (corrected p=112). The frequency of *BRAF*(^{V600E}) mutation was similar in patients with PTMC and PTC (65.6% vs. 67.2%). Immunohistochemical staining showed no different expression pattern according to the tumor size. These results suggest that PTMC is not an occult cancer and it can act like larger PTC. It is the authors' opinion is that PTMC should not be underestimated in practice.

Commentary

This is a major study that has clinical ramifications concerning the diagnosis and treatment of PTMC and PTCs, and perhaps most importantly, this study indicates that PTMC and PTC are an expression of the same tumor.

HIGHLIGHT SUMMARY

Clinical features that affect treatment, follow-up and outcome of PTMC

- Patient age affects the incidence rates of PTC and PTMC
- Autopsy studies have had a negative influence on the choice of therapy in patients with PTMC
- A 5-year follow-up of PTMC ≤1 cm without surgery is possible, but over time often requires surgery
- A 35-year follow-up of PTMC ≤1 cm may identify regional and distant metastases, and relapses
- 11-22 mm PTCs are likely to have a worse prognosis than PTMCs ≤10 mm
- ^{18}FDG-PET scans are effective for screening and detecting recurrences and metastases, but may create management dilemmas leading to unnecessary procedures and patient anxiety
- Small tumor size alone does not always assure low risk in incidentally identified thyroid cancers
- Incidental thyroid tumors usually require little or no therapy whereas non-incidental thyroid tumors usually require vigorous treatment

• Multifocal cancers are considered to have a poor prognosis because they are thought to be the result of intrathyroidal spread of PTC; however, a recent important study[59] has shown that PTMC does not differ from overt PTC in terms of demographics clinical-pathological features and *BRAF*^{V600E} mutation status, suggesting that PTMC is not a simple occult cancer that differs from larger PTCs, but instead can have behavior similar to larger PTCs.

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