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Managing the increasing diagnosis of papillary micro-cancer of thyroid

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There has been an increase in the incidence of thyroid cancer in the last decade, mainly due to the increase in imaging. A majority of the cases are for papillary cancers <1 cm. Mortality from thyroid cancer has stayed stable, thus, there is a large pool of papillary micro-cancer of thyroid in the general population without clinical significance. For these cancers a different approach is needed and active surveillance or less aggressive management should be offered as options. Controlled studies of minimally invasive procedures such as ethanol ablation are needed. If surgery is chosen, lobectomy alone should be adequate. Cases of occult papillary micro-cancer with local and distant metastases are very rare and should be managed according to the staging and risk category of the disease.

Papillary micro-cancer (PMC) is a low-risk thyroid cancer with the size <1 cm provided that histologic aggressive subtypes such as high-grade papillary cancer (PTC), columnar cell PTC, tall-cell PTC, trabecular PTC, cribriform-morular and hobnail variants [1] are excluded. However, most of these aggressive subtypes have different clinical presentations and are larger than 1 cm. PMC is usually discovered incidentally by imaging for other indications or by thyroid surgery done for benign disease.

There has been a worldwide increase in diagnosis of thyroid cancer in the last 10–15 years [2,3]. Reports from different countries and ethnic backgrounds show similar upward rates of diagnosis. Almost all of the increase in thyroid cancer is PMC. Although there is a possibility that environmental factors may contribute to a small portion of the increased incidence [4], overwhelming evidence suggests that increased diagnosis is mainly related to increased use of thyroid ultrasound or imaging done for other purposes [3,5]. Many studies have shown that mortality of thyroid cancer has stayed stable despite increased diagnosis. Thus, it can be concluded that most of the increase in thyroid cancer represents clinically insignificant disease [5,6]. In South Korea after initiation

of national screening for colon, lung and ovarian cancer many hospitals added ultrasound of thyroid for thyroid cancer screening. This resulted in fivefold increase in detection of thyroid cancers. However, there was no increase in mortality over these years [7], strongly suggesting that systematic screening will result in detection of occult thyroid cancers that carry no clinical significance.

The majority of papillary thyroid cancers that are <1 cm are found either on CT imaging, neck ultrasound, MRI or FDG-PET scans done for other purposes. Rarely, <1 cm lesions may be palpable on a lean neck, usually when located in the isthmus. Very rarely neck node metastases or distant metastases lead to the diagnosis of occult PMC cancers. In these cases the risk categories will be higher.

An epidemiologic study in Olmsted County Minnesota compared thyroid cancer rates in the years 1990–1999 to 2000–2012. The incidence increased from 7.1/100,000 to 13.7 without an accompanying increase in mortality. Of all thyroid cancers diagnosed, 53% were incidentally found and were asymptomatic. Exclusion of these incidentally discovered cancers reduced the rate to 6.3%, statistically not different from the incidence from previous decades [8].

EXPERT
REVIEWS

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There is ample evidence for existence of large pool of occult PTCs in the general population. A PubMed search of English literature that included reviews of 7897 autopsies from 21 countries revealed an average incidence of 7.6% PTC found in patients dying from other causes [9]. Even with a conservative estimate 7% of US population have occult thyroid cancer. Thus, 22 million will have PMC. With estimated cause specific thyroid cancer death rate of 1780 per year in the US, likelihood of death from thyroid cancer will be 79 per one million (0.0079%). Since almost all mortality is from cancers with clinical presentation, mortality would be close to zero for occult undiagnosed thyroid cancers.

Mayo experience with 900 PMCs seen over 60 years with a median size of 7 mm showed 0.3% distant metastases, 6% lymph nodal recurrence and only 0.3% cause specific mortality. Most of the recurrences were in multifocal tumors with initial neck lymph node positivity. Among the group, 99% were not at risk of distant spread or mortality. Radioactive iodine remnant ablation or bilateral lobectomy did not change the outcome [10]. In a report of 14,045 PMCs seen between 1986 and 2013 in Korea from a single institution, 10–20 year survival was 98 and 94% and disease-free 10–20 year survival was 97 and 94%. There was no difference in the outcome between total thyroidectomy and less than total thyroidectomy [11].

With all of the above considerations, a less aggressive approach for PMC is being proposed. These include active surveillance or limited intervention. If surgery is chosen, provided there is no extrathyroidal extension and no evidence of nodal disease, thyroid lobectomy will be adequate. History of prior head and neck irradiation and familial thyroid carcinoma syndromes should favor near total thyroidectomy. For PMCs found on thyroid surgery, no further intervention including radioactive iodine therapy is needed. If surgery was lobectomy, thyroxine therapy is not needed. Active surveillance should also be offered to patients with high surgical risk and complex medical conditions and in very old. Patient preferences should also be considered. A singer may consider observation and a healthy executive may choose surgery.

There are studies to show that active surveillance is safe for PMC. In a Japanese study, 1235 patients chose observation and were followed from 1993 to 2011. Progression was lowest in those over age 60 and highest in those younger than 40 years age group. Young age was independent predictor of progression. None of the 1235 patients had distant metastasis or died from thyroid cancer. Surgery was required in 6% of patients during follow-up. The authors concluded that the older patients with PMC are best candidates for observation. However, for younger patients it was not too late for curative surgery if progression was noted [12]. Some authors have expressed reservation for non-operative management of small PTCs that are <2 cm because in their review 12.3% of patients with cause specific mortality had lesions <2 cm [13]. However, these results do not apply to lesions <1 cm.

There are special situations when aggressive management is needed. If there is lymph node or distant metastases at presentation, near total thyroidectomy and radioactive iodine remnant ablation for Stages II (younger than 45) and Stages III and IV (older than age 45) will be recommended. Near total or total thyroidectomy is also needed for patients with history of head and neck radiation, aggressive histology, non-medullary hereditary differentiated thyroid cancer or in those with strong family history in first degree relatives. extrathyroidal extension of tumor in syndromic thyroid cancers such as Cowden, Carney complex and Wermer syndrome [14,15], indicates more aggressive approach. Some authors suggest that FDG-PET positive papillary thyroid cancer may be more aggressive [16]. However, in a study comparing incidental cancers found by FDG-PET and those with other types of imaging, FDG-PET positive incidental cancers were older and had more advanced TNM stages, most likely related to older age of the patients. After matching for age and sex none of the clinicopathologic features showed significant difference [17]. We feel that for this group more data are needed.

Ethanol ablation of unifocal PMC in the absence of any risk factors may be a consideration. This method has been extensively used in our institution for metastatic thyroid cancer in neck lymph nodes and has been safe and highly effective [18]. We have several patients with primary intra-thyroidal PMC treated with this method. We feel that in selected patients it may be used for primary unifocal PMC.

Unanswered questions remain. If lobectomy is done, should thyroxine therapy be initiated in view of possibility of micro-cancer in the other lobe and in the neck nodes? Should multifocal PMC be managed differently? Should non-invasive local ablation be considered for PMC? Should we avoid fine needle aspiration biopsy (FNA) for <1 cm suspected cancers and chose surveillance, especially in the elderly? Considering that a very small portion of PMCs may progress and have distant metastases, molecular markers that can diagnose this small subgroup are needed. At the present time although several markers such as BRAF [19], TERT [20] or TP53 [21] mutations are candidates, future studies are needed to clarify the role of molecular profiling in management.

In conclusion, the worldwide increase in incidence of papillary thyroid cancer is related to increased imaging and finding of non-significant PMCs. For PTC that is <1.0 cm, observation may be offered. One should consider morbidity of surgery compared to low probability of morbidity in untreated PMC. Controlled studies of observation versus surgery or minimally invasive procedure such as ethanol ablation are needed. If surgery is chosen for incidental PMC cancer, lobectomy should be adequate and central compartment lymph node sampling is not needed. For those that have chosen active surveillance if neck node metastases or progression occurs, patients are not harmed because of delay in surgery. One should also be aware that rare cases of PMCs with significant neck lymph node or distant metastasis exist. But they usually have different initial presentations.

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