Pertinent physical findings suggesting possible malignancy include vocal cord paralysis, cervical lymphadenopathy, and fixation of the nodule to surrounding tissue.

With the discovery of a thyroid nodule >1 cm in any diameter, a serum TSH level should be obtained. If the serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hyperfunctioning (''hot,'' i.e., tracer uptake is greater than the surrounding normal thyroid), isofunctioning (''warm,'' i.e., tracer uptake is equal to the surrounding thyroid), or nonfunctioning (''cold,'' i.e., has uptake less than the surrounding thyroid tissue) (44). Since hyperfunctioning nodules rarely harbor malignancy, if one is found that corresponds to the nodule in question, no cytologic evaluation is necessary. If overt or subclinical hyperthyroidism is present, additional evaluation is required. A higher serum TSH level, even within the upper part of the reference range, is associated with increased risk of malignancy in a thyroid nodule, as well as more advanced stage thyroid cancer (45,46).

[A5] Serum thyroglobulin measurement

■ **RECOMMENDATION 3**

Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended.

(Strong recommendation, Moderate-quality evidence)

Serum Tg levels can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer (47–49).

[A6] Serum calcitonin measurement

■ **RECOMMENDATION 4**

The panel cannot recommend either for or against routine measurement of serum calcitonin in patients with thyroid nodules.

(No recommendation, Insufficient evidence)

The utility of serum calcitonin has been evaluated in a series of prospective, nonrandomized studies (50–54). These data suggest that the use of routine serum calcitonin for screening may detect C-cell hyperplasia and MTC at an earlier stage, and overall survival consequently may be improved. However, most studies relied on pentagastrin stimulation testing to increase specificity. This drug is not available in the United States, Canada, and some other countries, and there remain unresolved issues of sensitivity, specificity, assay performance, cut-offs using calcium stimulation (55), and cost effectiveness. Two retrospective studies have shown improved survival in patients diagnosed with MTC after routine calcitonin testing compared with historical controls (53,56), but they were unable to show a decreased number of MTC-related deaths. A cost-effectiveness analysis suggested that calcitonin screening would be cost effective in the United States (57). However, prevalence estimates of MTC in this analysis included patients with C-cell hyperplasia and microMTC, which have uncertain clinical significance. Based on the retrospective nature of the survival data, unresolved issues of assay performance, lack of availability of pentagastrin in North America, and potential biases in the cost-effective analysis, the task force cannot recommend for or against the routine measurement of serum calcitonin as a screening test in patients with thyroid nodules, although there was not uniform agreement on this recommendation. There was, however, agreement that serum calcitonin may be considered in the subgroup of patients in whom an elevated calcitonin may change the diagnostic or surgical approach (i.e., patients considered for less than total thyroidectomy, patients with suspicious cytology not consistent with PTC). If the unstimulated serum calcitonin determination has been obtained and the level is greater than 50–100 pg/mL, a diagnosis of MTC is common (58).

There is emerging evidence that a calcitonin measurement from a thyroid nodule fine-needle aspiration (FNA) washout may be helpful in the preoperative evaluation of patients with a modestly elevated basal serum calcitonin (20–100 pg/mL) (59).

[A7] [^{18}F]Fluorodeoxyglucose positron emission tomography scan

■ **RECOMMENDATION 5**

(A) Focal [^{18}F]fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) uptake within a sonographically confirmed thyroid nodule conveys an increased risk of thyroid cancer, and FNA is recommended for those nodules ≥1 cm.

(Strong recommendation, Moderate-quality evidence)

B) Diffuse ^{18}FDG-PET uptake, in conjunction with sonographic and clinical evidence of chronic lymphocytic thyroiditis, does not require further imaging or FNA.

(Strong recommendation, Moderate-quality evidence)

^{18}FDG-PET is increasingly performed during the evaluation of patients with both malignant and nonmalignant illness. While ^{18}FDG-PET imaging is not recommended for the evaluation of patients with newly detected thyroid nodules or thyroidal illness, the incidental detection of abnormal thyroid uptake may nonetheless be encountered. Importantly, incidental ^{18}FDG-PET uptake in the thyroid gland can be either focal or diffuse. Focal ^{18}FDG-PET uptake in the thyroid is incidentally detected in 1%–2% of patients, while an additional 2% of patients demonstrate diffuse thyroid uptake (60–62).

Focal thyroid uptake most often corresponds to a clinically relevant thyroid nodule, and US examination is thus recommended to define thyroid anatomy. Importantly, focal ^{18}FDG-PET uptake increases malignancy risk in an affected nodule, and therefore clinical evaluation and FNA of nodules ≥1 cm is recommended. ^{18}FDG-PET positive thyroid nodules <1 cm that do not meet FNA criteria (see Recommendation 8) can be monitored similarly to thyroid nodules with high-risk sonographic patterns that do not meet FNA criteria (see Recommendation 24A). A recent meta-analysis confirmed that approximately one in three (~35%) ^{18}FDG-PET positive thyroid nodules proved to be cancerous (60), with higher mean maximum standardized uptake value in malignant compared to benign nodules (6.9 vs. 4.8, $p < 0.001$). In contrast, diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake in the setting