AGENCY FOR HEALTHCARE RESEARCH AND QUALITY

TECHNOLOGY ASSESSMENT

SYSTEMATIC REVIEW OF

POSITRON EMISSION TOMOGRAPHY

FOR FOLLOW-UP OF TREATED THYROID CANCER

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EXECUTIVE SUMMARY

Background. Patients with treated thyroid cancer are followed routinely to look for metastatic disease. For most tumor types, patients can be followed by serum biomarkers, such as thyroglobulin for differentiated cancer or calcitonin for medullary cancer, which indicate the likely recurrence of thyroid cancer. To confirm and localize the tumor recurrence or metastasis an imaging study is used, such as ^{131}I scintigraphy (WBS) for differentiated cancer or computed tomography, somatostatin receptor scintigraphy (SRS), or magnetic resonance imaging for medullary cancer. However, these standard imaging tests may be negative in the face of biochemical evidence of metastatic disease. Positron emission tomography (PET) has been proposed as a highly accurate test to detect metastatic disease in this setting. However, PET is expensive, is not commonly available, and may not be sensitive for metabolically inactive tumors.

Questions of interest. 1. What is the test performance of PET for localization or staging of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease? 2. In the same population, what is the evidence that PET affects health outcomes or alters management? 3. What are the test performance and effect on clinical

management of PET for initial, pre-treatment, staging of patients differentiated thyroid cancer types that commonly do not take up radioiodine?

Methods. We conducted a comprehensive Medline search for English-language literature. Additional articles were found from references of reviewed articles. Search terms included those related to PET scan and thyroid cancer. Included were studies that reported on diagnostic performance of PET or clinical outcomes of subjects who had PET. Studies of differentiated thyroid cancer with fewer than 10 subjects were excluded. Studies of medullary and other rare thyroid tumors were included regardless of sample size due to the scarcity of larger studies. When feasible, test performance was plotted for visual inspection and combined sensitivity and specificity were calculated.

Results. Eleven studies met criteria to evaluate test performance of PET to diagnose metastatic differentiated thyroid cancer. Across the studies sensitivity ranged from 62% to 100% and specificity ranged from 0% to 100%. The two studies that reported on at least 10 subjects each to provide estimates of both sensitivity and specificity reported sensitivity of 88% and 96% and specificity of 100% and 73%, respectively. Because of the variability of results among the studies, combined estimates of test performance across the 11 studies are not reliable. Six studies met criteria to evaluate test performance of PET to diagnose metastatic medullary thyroid cancer. All were small and no reliable

estimate of PET test performance could be made. Six peer reviewed studies (and one letter) reported data on effect of PET on clinical management or outcomes of differentiated thyroid cancer. Among the studies, about 80% of subjects had treatment of metastatic disease after positive PET; about 20% had no change in clinical management. In most studies, it is unclear whether treatment decisions were influenced by PET results. About one-third of subjects had reported cure after positive PET and one-third had recurrence of cancer; no data were provided on the remaining subjects. Duration of follow-up was generally brief or not reported. Data reporting was generally incomplete, making proper analysis difficult. Two studies reported data on effect of PET on clinical management or outcomes of medullary thyroid cancer. Of 9 subjects, 3 had reported surgical cure. No data were reported on duration of follow-up. Insufficient data have been reported about PET for rarer forms of thyroid cancer to draw conclusions.

Conclusions. Only two studies were sufficiently powered to provide potentially reliable estimates of PET sensitivity and specificity for diagnosing metastatic disease in patients with treated differentiated thyroid cancer, elevated thyroglobulin, and negative WBS. Sensitivity was 88% and 96%; specificity was 100% and 73%, respectively. However, the poor quality and small size of these studies limit the reliability of the test performance estimates. Smaller

studies reported wide ranges of sensitivity and specificity. Insufficient data exist to estimate the test performance of PET for treated medullary thyroid cancer or other rarer forms of thyroid cancer. Limited data suggest that PET may affect management of patients with differentiated cancer and may result in cure of at least one-third of such patients. However, study quality was too poor and follow-up duration was too short (or not reported) to allow a definitive conclusion. Insufficient data exist to estimate the effect of PET on treatment management of patients with medullary or other rarer forms of thyroid cancer. Overall study quality was poor and study sample sizes were small. Future well-designed, clearly reported studies that focus on patients with treated thyroid cancer, elevated biochemical markers of metastasis and negative standard imaging tests are needed to define test performance and effect on clinical management and outcome of PET.

INTRODUCTION

Evaluation of Patients Suspected to Have Metastatic Thyroid Cancer

Patients with epithelial thyroid cancer or medullary thyroid cancer require evaluation of the extent of disease in order to determine management. Prior to definitive treatment, staging occurs to determine the spread of the cancer. After initial treatment patients are generally followed for possible local recurrence or distant metastasis of disease. Positron emission tomography (PET) has been proposed for use in both initial and post-treatment staging of thyroid cancer.

Epithelial thyroid cancers are divided into differentiated carcinomas (papillary and follicular) and anaplastic carcinomas. Most differentiated carcinomas secrete thyroglobulin (Tg) and take up iodine. Thus Tg level and ^{131}I whole body scintigraphy (WBS) are commonly used to look for metastases of this tumor. (1) However, metastases of differentiated thyroid cancer are less efficient at iodine uptake than normal thyroid tissue and less than 50% of papillary and about 33% of follicular thyroid metastases can be imaged with radioactive iodine. (2) Certain subtypes of differentiated carcinomas, including Hürthle cell tumors, are less likely to take up iodine. (2) The evaluation of patients with poorly differentiated insular, tall cell and columnar variants of papillary cancer, and anaplastic (undifferentiated) thyroid cancers is

complicated by the lack of tumor markers or variability of radioisotope uptake. (3;4)

For patients with medullary thyroid cancer, calcitonin and/or carcinoembryonic antigen (CEA) levels are followed to indicate the presence of metastatic disease. (1) However, further evaluation of patients with elevated calcitonin levels following operative resection is challenging since in many patients the use of multiple imaging modalities fails to localize the metastatic disease. (1)

Patients with biochemical evidence of metastatic disease generally have imaging tests performed to localize metastases. If the imaging test -- WBS for differentiated thyroid cancer or computed tomography, somatostatin receptor scintigraphy (SRS), magnetic resonance imaging, ultrasonography or other tests for medullary or less well differentiated tumors -- is non-diagnostic, there is no consensus on the next level of appropriate test. PET has been proposed as a highly accurate test to detect metastatic thyroid cancer.

PET is a nuclear medicine imaging technique that uses radiopharmaceuticals, typically a radionuclide-labeled analogue of glucose, 2-[^{18}F] fluoro-2-deoxy-D-glucose (FDG), to detect abnormal metabolic activity within the body. Since malignant tumors usually have increased cellular metabolism, and thus increased glucose metabolism, PET is able to localize

malignant tissue. By providing information on function and metabolism, PET may complement traditional imaging modalities such as plain-film radiography, computed tomography (CT) and magnetic resonance imaging (MRI), which provide anatomical information of both normal and abnormal structures. In addition to being able to distinguish benign from malignant processes based on differences in biological activity, PET has the advantage of being able to examine the whole body for both primary and metastatic disease in a single procedure. (5)

PET has the disadvantages of being expensive and not commonly available. Furthermore, FDG PET will not detect tumors that do not take up glucose, must be used with care in diabetics, and is unlikely to detect metastatic brain masses (due to the high uptake of glucose by brain tissue).

FDG PET has been proposed for use in the evaluation of patients with evidence of metastatic differentiated and medullary thyroid cancer with non-diagnostic imaging tests, as well as in the initial staging of thyroid cancer prior to treatment. A HCFA (now CMS) public hearing was held in 2000 to discuss coverage of PET for a broad range of uses, including thyroid cancer. CMS is currently evaluating the use of PET for thyroid cancer and has requested assistance from AHRQ in evaluating the available evidence.

Specific questions of addressed are:

1. What is the test performance of FDG PET for localization or staging of previously treated thyroid cancer suspected to be metastatic (due to elevated biochemical marker or to tumor type) for which standard imaging modalities (scintigraphy, ultrasonography, computed tomography, magnetic resonance imaging) have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease (such as Hürthle cell thyroid cancer, histological variants of thyroid cancer such as tall-cell or insular subtypes, and other poorly differentiated thyroid cancers which may take up iodine poorly)?
2. What is the evidence that FDG PET affects health outcomes (survival, cancer recurrence, quality of life) or alters management when used for localization or staging of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease?

A third question related to the utility of PET in the initial staging of thyroid cancers known to concentrate iodine poorly. This topic was not addressed because only one study, which reported on only 1 subject with Hürthle cell cancer, addressed this issue. (6)

METHODS

Literature search

A systematic literature search was performed to identify relevant articles on PET scans and thyroid cancer. The search was supplemented by articles in reference lists of relevant articles and reviews.

A Medline literature search was performed on Sept 28, 2001 (1966 - September Week 3 2001) to capture primary studies that investigated the use of PET scans for thyroid cancer. The Medline search was supplemented by searches in Biosis and CancerLIT. See Table 1 for search strategy used. The search strategy found studies on thyroid, thyroid cancer or thyroid cancer markers, which were also on PET and related technologies. The goal of the search was to be highly sensitive, to capture as many relevant articles as possible. Relevant keywords from articles found from preliminary searches (eg, Medline registry numbers for FDG) were added to broaden the search results. The search was limited to English-language studies of human subjects. Studies prior to 1980 were excluded as PET did not exist prior to this.

The abstracts and titles from the literature search were screened for potentially relevant articles. We retrieved and reviewed relevant primary and review articles. We extracted data from primary studies of the diagnostic performance or clinical outcomes of PET for previously treated thyroid cancer.

Thyroid cancer classification

Studies were divided into those that evaluated subjects with epithelial thyroid cancer and those that evaluated subjects with medullary thyroid cancer. Studies that evaluated subjects with both tumor types were included in both sections. Among studies of epithelial tumors, subjects that were reported to have follicular, papillary, mixed follicular-papillary, differentiated, well-differentiated, or Hürthle cell cancers were analyzed together as differentiated thyroid cancer. Those with Hürthle cell tumors were also analyzed separately. Subjects with other epithelial tumors that may concentrate iodine poorly were analyzed separately. All subjects with medullary cancer were analyzed together.

Eligibility criteria

Studies of diagnostic performance or clinical effect of PET for all types of thyroid cancer were included. Diagnostic studies had to evaluate the test performance of PET to differentiate subjects with metastatic thyroid cancer from those without metastatic disease; sufficient data were required to estimate PET sensitivity and specificity. Studies had to include either data on final diagnosis (outcome) or on disposition of subjects based on lesion histology or clinical follow-up. Thus diagnostic studies that reported only the positive and negative rate of PET or only compared the rate of positive PET to positive

WBS or other imaging tests were excluded. No study was rejected based on the reference standards used.

Studies of differentiated thyroid cancer had to evaluate at least 10 subjects. While it would have been preferable to include only studies that included at least 10 subjects with and 10 subjects without metastatic disease, this would have resulted in having too few qualifying studies. Because only one study of PET for other thyroid cancers (medullary, anaplastic) included more than 10 subjects and because of the small total number of such studies, all were included, regardless of sample size. Review articles of PET and thyroid cancer were examined for additional references and for background information.

In general, only studies that reported either test performance data or clinical outcome data on PET specific to samples of subjects who were within the populations of interest were included. These included subjects with either 1) treated differentiated thyroid cancer, elevated Tg or anti-Tg antibody, and negative WBS, 2) treated medullary thyroid cancer, elevated calcitonin or CEA, and negative standard imaging, or 3) untreated differentiated thyroid cancer types that commonly do not take up radioiodine. We did not define “standard imaging” *a priori*, but used each study’s definitions as implied by what imaging test results were reported. Studies reporting data on any rare form of thyroid

cancer, regardless of prior testing, were included. Studies were not excluded based on any quality criteria.

To focus on the value of PET in patients with differentiated thyroid cancer in the setting of elevated marker and negative WBS, we ignored the results of imaging tests for differentiated cancer other than WBS and PET (when reported). While in clinical practice PET or other imaging studies may not be necessary for a patient with a negative WBS but a positive bone scan, we aimed to make our findings as generalizable as possible by not considering less commonly used imaging tests for differentiated cancer. Furthermore, few studies sufficiently reported on other imaging tests to allow us to summarize only those subjects with all imaging tests negative.

Estimating overall test performance

For analysis of differentiated thyroid cancer studies (for which there were sufficient data), we used two different methods to summarize the test performance of PET: plotting studies in receiver operating characteristics (ROC) space, and separately averaged sensitivity and specificity values across studies. For analysis of medullary thyroid cancer studies (for which there were minimal data), we calculated a combined test performance by simply adding the data across studies.

In the ROC analysis, each study provides a pair of sensitivity and specificity values. Individual studies are plotted with the sensitivity on the x-axis and 100%-specificity on the y-axis. Studies with better test performance (higher sensitivity and specificity) will fall closer to the upper left corner.

To determine an estimate of overall test performance for differentiated thyroid cancer we combined test performance data to calculate average sensitivity and specificity across studies. We used a random effects model which weights studies by both within-study variation (sampling error) and between-study variation (true treatment-effect differences). It gives wider confidence intervals than the fixed effects model, which includes only within-study variation, and is thus a more conservative estimate of test performance. In addition to error due to chance, the random effects model also accounts for error due to heterogeneity among studies. Combined sensitivity and specificity are calculated independently.

When each value is combined separately, sensitivity and specificity tend to underestimate the true sensitivity and specificity. While this method treats sensitivity and specificity as independent, in reality, the two are inversely related to each other; as the test threshold is varied to increase sensitivity, specificity falls, and vice versa. Furthermore, the value of the combined estimates should be interpreted with caution in cases where there is wide

variability in test results from different studies. The independently combined estimates using the random effects model may nonetheless be useful estimates of the average test performance.

RESULTS

Literature Search

The literature search yielded 1,392 citations -- 1,390 from Medline, 2 from Biosys, 0 from CancerLIT (Table 1). Of these, 41 reported data on PET and treated thyroid cancer, (3;7-46) one reported on a single subject with untreated atypical (Hürthle cell) cancer. (6) Nine studies with fewer than 10 eligible subjects with differentiated cancer were excluded; (3;26-33) although three of these that reported data on rare tumor types were included for the appropriate section. (3;26;27) Eight studies of differentiated or medullary cancer were not included because they did not report sufficient data to determine results specifically for the populations of interest. (34-41) Four articles were not included because they reported duplicate data as other articles and provided no additional information. (42-45) One study was excluded because there were no data on final diagnosis or disposition. (46) The remaining 19 reported data on either treated differentiated or medullary cancer with elevated marker and negative initial imaging test. (7-25)

Two articles reported on subsets of other larger articles, but unique data were provided in these articles. (10;45) The unique information is included in the description of the larger articles. One article from Germany was a multicenter study. (7) It is likely that this study includes subjects who had previously been reported in six other articles, most of which did not report sufficient data on Tg levels or WBS results on enough subjects to be included in this report on their own. (13;26;29;34;38;46) Furthermore, all the German articles share some authors. While some of these studies were clearly independent of some others, it is impossible to be sure from reading the articles that all these studies were independent of each other.

Primary Studies

Differentiated thyroid cancer, Elevated Tg, Negative WBS

Eleven studies reported data about PET on 10 or more subjects with previously treated differentiated thyroid cancer who had elevated Tg and/or elevated anti-Tg antibody and negative WBS. (7-10;14-20;42;45) Three of these studies included subjects reported in other articles (10;42;45) (Tables 2-4, Figure 1). These studies reported on 10 to 65 subjects with differentiated thyroid cancer, elevated biomarker and negative WBS. Reporting of the results of other imaging studies were generally incomplete. A total of about 244 relevant subjects were included. The demographics of the studies were similar:

the age ranges were generally about 20 to 70 years, with mean ages of about 40 to 50 years, and two-thirds or more of the subjects were female. In general, about 60% to 70% of differentiated thyroid cancers were papillary and 30% to 40% were follicular. Two studies included only subjects with papillary cancer. (9;18)

Only two studies were clearly prospective; (8;14) a third was probably prospective. (17) Most studies were vague about the definition of a positive PET scan, with descriptions such as focal or pathologic uptake of FDG. Only one study gave a quantitative threshold for a positive scan. (9) Five studies reported that scans were interpreted independently by two experienced physicians; the remaining did not provide data on scan interpretation. Only one study reported that the PET readers were blinded to clinical data. (8). The methods used to determine final patient status varied considerably across studies. In general, multiple methods including histology, imaging and clinical follow-up were used. Two studies explicitly included Tg levels as part of the method of diagnosing subjects; one study did not provide data on the method of diagnosing subjects.

Test Performance

Eleven studies reported on the test performance of PET to diagnose (and localize) metastatic differentiated thyroid cancer explicitly in patients with prior

surgical and ablation therapy who had elevated Tg or anti-Tg antibodies but negative WBS in 10 or more subjects. (7-10;12-18) However, Grunwald, (1999) may include subjects previously reported in Grunwald (1997). These studies included about 244 subjects (two studies had incomplete data reporting, see Table 3 (9;13)).

Sensitivity ranged from 62% to 100%; specificity varied between 0% and 100% (Table 3, Figure 1). Due to the small sample sizes, the confidence intervals for the test performance estimates are wide. In particular, almost all studies had small numbers of subjects without metastatic disease. Only one study had as many as 25 subjects without metastases. (7) The other studies all had 11 or fewer subjects without metastases. These small numbers make estimates of specificity unreliable. Overall, there were no clear relationships between estimated test performance and either study size or prevalence of metastatic disease.

Using a random effects model to calculate the average sensitivity and specificity across studies, the combined sensitivity was 84% (95% confidence interval 73%-91%) and the combined specificity was 56% (95% confidence interval 27%-82%). For the analysis, the subject in Chung (2000) with a false positive study was included; subjects with either elevated Tg or anti-Tg antibody in Wang (1999) were included. Frilling (2000), which did not have

subjects without metastatic disease, and Grunwald (1997), which had incomplete data were excluded. Because of a number of factors, including small sample size, heterogeneity of study samples, and wide variation in the test performance estimates among different studies, the combined test performance data calculated should be considered at best a preliminary estimate, and should be interpreted with caution.

Only two studies had at least 10 subjects in both with and without metastatic disease groups. (7;8) These two studies are listed in bold in Table 3 and are represented by the larger black ovals in the figure. Both studies found relatively high sensitivity (88% and 96%). Specificity in both studies was higher than in most smaller studies (100% and 73%).

Clinical outcomes

Reporting was generally incomplete on the effect of PET on clinical outcomes or management in subjects with differentiated thyroid cancer in patients with prior surgical and ablation therapy who had elevated Tg or anti-Tg antibodies but negative WBS (Table 4). Seven studies provided some information on relevant patients. (8;10;15-18;20) Four of the seven studies reported that biopsies were performed on 9% to 100% of subjects with (true or false) positive PET; overall, 34% of subjects had biopsies. Five of the seven studies reported that 27% to 97% of subjects had surgery and/or radioiodine

ablation based on positive PET scans; overall, 71% of subjects in the five studies had treatment based on positive PET scans. Lind (2000) reported that therapeutic strategy was changed in “most” of 48 subjects who had PET scans. (20) Four of the seven studies reported that 0% to 48% of subjects had successful treatment and/or reported cure based on positive PET; overall, 33% of subjects in the four studies had reported cure. Three of the seven studies reported that 0% to 85% of subjects had recurrence; overall 34% of subjects in the three studies treated after positive PET had recurrence of disease. However, definitions of cure, recurrence and duration of follow-up were not consistent and were generally inadequately reported. Five of the seven studies provided sufficient data to estimate the number of subjects who had no change in management despite positive PET. Between 3% and 92% of subjects had no change in management; however in a case series reported in a letter to the editor, PET was explicitly ignored in determining patient management. (16) Excluding this letter, overall, 21% of subjects in the remaining four studies had no change in management based on a positive PET. Management was not changed by PET results because of patient decision in 2 subjects and the determination that the PET was falsely positive in 4 subjects. No explanation was given for no change in management for the remaining subjects. Three of the seven studies reported data on the disposition of 17 subjects with positive

PET who did not have a change in management (49% of subjects with positive PET). (10;15;16) Fourteen had no further disease (4 explicitly had false positive scans), 2 had diffuse disease, 1 had limited disease at follow-up.

No study reported clinical outcome data specifically on patients with differentiated thyroid cancer subtypes that poorly concentrate iodine. No study evaluated the incremental or relative value of PET over other imaging tests in regards to clinical outcomes.

Medullary thyroid cancer, Elevated calcitonin, Negative imaging studies

Seven studies reported data about PET on subjects with treated medullary thyroid cancer, elevated calcitonin (and elevated CEA in three studies) and negative other imaging tests. (19-25) The exact battery of imaging tests performed varied from study to study and subject to subject. (See Table 2, Part III, Comments) These studies reported on 1 to 8 subjects who met the above criteria. A total of 25 subjects were included.

Two studies were prospective (21;22); five were retrospective (one was a case report). Definitions of positive PET varied, including focal or increased uptake of FDG or no data. Only one study gave a quantitative threshold for a positive scan. (24) Three studies reported that scans were interpreted independently by two or three experienced physicians; the remaining did not

provide data on scan interpretation. Only two studies reported that the PET readers were blinded to clinical data. (21;24) The methods used to determine final patient status generally included surgery and histopathology and clinical follow-up data. The follow-up data were frequently difficult to interpret; it was not always clear whether subjects were considered to have metastatic disease or not. One study did not provide data on the method of diagnosing subjects.

Test Performance

Six of the seven studies reported on the test performance of PET to diagnose (and localize) metastatic medullary thyroid cancer in patients with prior surgical treatment who had elevated calcitonin (and possibly CEA) but negative standard imaging tests. (19;21-25) The studies were all small, ranging from 1 to 6 subjects (Table 5). A total of 17 subjects were included. Test performance results were calculated for each study, although the meaningfulness of the values are questionable given the small size and the difficulty in assigning individual subjects to test performance categories. As noted in Table 5, unclear assignments include 1 subject with both a false positive lesion and a separate false negative lesion, (23) 1 subject for whom a true final diagnosis is not reported, (19) and one report where the text results differ from the table results. (24)

Because of the small study sizes and the fact that three of six studies have no subjects without metastatic disease, combining the data using a random effects model is not feasible. By simply adding together all subjects who had true positive, false negative, true negative and false positive PET scans, we calculated a sensitivity of 92% (N=13) and a specificity of 50% (N=4). A final diagnosis of metastatic disease was assigned to 76% of the subjects. The method for combining test performance data among these studies is highly flawed. Therefore, these results must be interpreted as preliminary, speculative estimates.

Because of the small numbers of studies and subjects, Table 5 also presents test performance data for subjects with treated medullary cancer and elevated calcitonin levels, regardless of results of other imaging tests. Note that four of these studies also reported data for those patients with negative imaging tests.

Two studies reported complete data on both PET and SRS with ^{111}In pentetreotide (octreotide) for subjects with previously treated medullary cancer. (21;22) The two studies were performed by the same study group and included 13 subjects with medullary cancer and elevated calcitonin or CEA. Twelve subjects had positive PET; 62 lesions were identified. SRS was positive for only one lesion in 1 subject. The remaining subjects had negative SRS. The

positive PET results were confirmed at surgery in 7 subjects. Confirmation of the remaining 5 subjects occurred at 1 year, but the method of confirmation was unclear. In one of these studies, 2 of the 7 subjects with medullary cancer and positive PET also had positive ^{99m}Tc dimercaptosuccinic acid (DMSA) scintigraphy. (21) The remaining 5 subjects had negative DMSA. One of the subjects with positive DMSA also had positive SRS.

Clinical outcomes

Reporting was generally incomplete on the effect of PET on clinical outcomes or management in subjects with medullary thyroid cancer in patients with prior surgical treatment who had elevated calcitonin (and CEA) but negative standard imaging tests (Table 6) Only two studies provided data on relevant patients. (20;25) In one study with 8 subjects, 2 subjects had reported surgical cure based on a positive PET scan; 6 subjects with distant metastases had no change in management based on PET scan. (20) Follow-up duration was not reported and no data were provided on the number of positive PET scans. In a case report, 1 subject with a positive PET had a reported surgical cure based on the PET scan. (25) Follow-up duration was not reported.

Because of the small numbers of studies and subjects, Table 6 also presents clinical outcome data for subjects with treated medullary cancer and

elevated calcitonin levels, regardless of results of other imaging tests. Five additional studies are included.

No study evaluated the incremental or relative value of PET over other imaging tests in regards to clinical outcomes.

Atypical tumor types

Hürthle cell tumors

Four studies provided data on subjects with differentiated thyroid cancer, elevated Tg, and negative WBS. They included 21 subjects with Hürthle cell tumors. (8;11;16;26) Test performance data were reported for only 8 of these subjects. Among all studies of PET and thyroid cancer, 49 subjects with Hürthle cell tumors are included in seven studies. (7;8;11;16;26;37) Only one study specifically analyzed PET test performance for Hürthle cell tumors. (7) Twenty subjects had Hürthle cell tumors; 2 had positive WBS, 18 had negative WBS. Sensitivity was 87% (among 15 subjects with metastatic disease); specificity was 100% (among 5 subjects without metastatic disease). No study provided clear data on the effect of PET on clinical outcomes in subjects with Hürthle cell tumors.

Poorly differentiated tumors

Only one study analyzed data based on tumor grade of differentiated thyroid cancer, although the grading system used has not been validated. (7) The study included 67 subjects with known tumor grade. No data were provided about Tg level for these subjects. Twenty-nine percent of subjects with poorly differentiated tumors (grade G2 or higher) had positive WBS; 21% of subjects with well-differentiated tumors (grade G1 or G1-2) had positive WBS. For those with poorly differentiated tumors, PET sensitivity was 76% and specificity was 82%. For those with well-differentiated tumors, PET sensitivity was 66% and specificity was 100%. The study explains the lower sensitivity for PET to diagnose well-differentiated metastases compared to poorly differentiated metastases by the slow growth, and therefore lower glucose use, of the well-differentiated tumors.

Anaplastic tumors

Three studies reported PET data on 7 subjects with anaplastic thyroid tumors. (11;20;27) One study found that for 4 subjects with anaplastic thyroid tumor, “the extent of the disease was demonstrated much better by FDG PET than by other diagnostic procedures. However, in none of these patients FDG PET changed the therapeutic strategy.” (20) No data specific to PET in the 3 subjects with anaplastic tumor were reported in the other papers.

Other tumor types with potentially variable radioisotope uptake

One study reported 4 subjects with “eosinophilic carcinomas” (3 had elevated Tg, 1 with abnormal ultrasonography; 1 had negative WBS, 1 had equivocal WBS, 2 did not have WBS). (12) For these subjects, PET was true positive in 2 and false negative in 2.

One study reported 1 subject with a tall cell papillary thyroid cancer (who had elevated Tg and negative WBS) who had a true positive PET. (15)

A case report of a subject with insular thyroid cancer who had elevated Tg, a positive WBS, and MIBI scan and subsequently had a negative PET, which was treated as if it were a false negative.

False Positive PET Scans of Differentiated and Medullary Thyroid Cancer

Among the reviewed articles, nine studies had 33 subjects reported to have false positive PET scans (Table 7). (7-10;13;15-17;23) Of these, 15 subjects had treated differentiated cancer, elevated Tg (as defined within each study) and negative WBS. One had treated medullary cancer, elevated calcitonin, and negative standard imaging. The remaining subjects had other imaging tests prior to PET that were positive for metastases.

PET results were reported to be false positive based on biopsy or surgical material in 14 of the 33 subjects. Eight had negative or normal histological specimens (including 1 subject with both false positive and false negative lesions). Three subjects had inflamed cervical lymph nodes, 1 had

granulomatous inflammation, 1 had fibrous dysplasia, and 1 had tuberculosis. Of the remaining 19 subjects, 11 in one study were classified as false positives based on a combination of histology, Tg level, US, CT, and observation. (7) In 6 of the remaining subjects, including 1 with a non-diagnostic biopsy, PET was classified as false positive based on follow-up MRI, CT, US, plain chest radiography, and/or observation. The duration of clinical follow-up was generally not reported. Two other subjects were reported to have false positive PET due to inflammation of a tracheostomy and thymus uptake, although the method of determining these diagnoses were not reported.

Three subjects (9%) had CT or ultrasonography (US) that were consistent with PET, and were also false positive [Alnafisi (2000), FP 3, FP 4; Wang (1999), FP 1. See Table 7]. Two subjects had false positive lung lesions on CT and either a false positive thyroid or humerus lesion on PET [Alnafisi (2000), FP 2; Wang (1999), FP 3]. Ten subjects had other imaging studies (CT, MRI, US) that were true negatives. The studies did not report data on other imaging studies (other than WBS) in 18 subjects. One subject with medullary cancer had one lesion on PET that was a false positive, but also was found to have metastatic disease on cervical lymph node dissection that was missed on CT [Musholt (1997), FP 1/FN 1].

False positive lesions were seen in cervical lymph nodes in 11 subjects (44%), thyroid in 4 subjects (16%), mediastinum in 3 subjects (12%), lungs in 2 subjects (8%) and one lesion each (4%) in the spine, pharynx, humerus, tracheostomy, and “distant.” Location was not noted in 11 subjects. Some subjects had false positive lesions in multiple locations.

DISCUSSION

Limitations due to study quality

The quality of the studies and the value of their reported data are limited by a number of factors. Only two studies were prospective in design and included only subjects with biochemical evidence of metastasis and negative imaging tests. Of these only one met minimal criteria to reliably estimate test performance (10 subjects in both metastatic disease and no metastatic disease arms). Most other studies were retrospective case series. Some were clearly biased samples of the authors’ experiences with PET. In addition most studies included mixed populations of subjects with different disease types and different underlying likelihood of metastatic disease. No study of differentiated thyroid cancer included a sub-analysis of the value of PET in patients with negative WBS and other standard imaging tests (eg, CXR, CT, MRI, US). Studies of medullary thyroid cancer used widely different batteries of “standard” imaging tests prior to PET.

Most studies did not limit eligible subjects to those for whom PET is most likely to be of value, eg, those at higher risk of metastasis based on biochemical tests (Tg or calcitonin) but who have a negative imaging work-up. Therefore much of the data for this report are based on sub-group analyses or, more frequently, individual subjects from broader studies who fit the criteria of this report. These data, in general, are unreliable as they rely on incomplete and unclear reporting. Furthermore, no study explicitly examined the incremental value of PET over other imaging tests.

Furthermore, most studies had small sample sizes. Only two studies of differentiated thyroid cancer had minimally sufficient sample sizes for potentially reliable estimates of both sensitivity and specificity. For studies of medullary cancer, no study had at least 10 subjects who met criteria for this report. Studies that reported on rarer tumors were all too small to provide reliable estimates of test performance.

Blinding of PET interpreters to clinical data was infrequent. Only five studies reported that blinding occurred. Unblinded studies are less reliable since the interpretation of the PET scan may in part be based on other clinical data. This is especially the case for these studies as many included subjects had other positive imaging tests. This problem is further compounded by the fact that most studies used vague or qualitative definitions of positive PET

scan, such as increased or abnormal FDG uptake. These definitions allow subjective test interpretation that may be more susceptible to bias based on known clinical data. Only rarely did studies used quantitative standardized uptake values (SUV) to define positive tests, but even some of these combined SUV data with qualitative definitions (eg, SUV threshold or abnormal uptake of FDG).

Reference standards (the definition of whether a subject truly has or does not have metastatic disease) were rarely well defined. All studies (except one with no data) used histology from biopsy or surgery to diagnose at least some subjects with positive PET. Some studies also used exploratory surgery to diagnose some subjects with negative PET. Most relied on clinical follow-up to diagnose subjects with negative PET. However, none gave a clear description of how final diagnoses were made clinically. In addition, many relied on other imaging tests and even changes in Tg or calcitonin levels. Some used clinical follow-up to determine a final diagnosis even for some subjects with positive PET. Few studies reported the duration of clinical follow-up. Most of those that did, had short duration of follow-up (less than 3 years). For many studies, the definitions of reference standards were unclear and it was thus difficult to assign subjects as either positive or negative for metastases.

Another source of possible bias is funding source. Of note, no study reported the source of study funding. While this is a common omission, it is of particular concern for the evaluation of a technology that has a high capital expense, a high per test cost, and that is not routinely available or paid for.

Finally, there was considerable duplication of data due to multiple publications on the same study samples. While most of these duplications were easy to discover, the largest study most likely includes many subjects from multiple previously reported studies. The study neither acknowledged the other studies nor clearly stated the source of their study sample.

Findings

Test performance of FDG PET for localization or staging of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease.

Eleven studies with at least 10 subjects each (total of 244 subjects) reported test performance data in subjects with treated differentiated thyroid cancer, elevated Tg, and negative WBS. The largest study included 65 subjects who met these criteria. (13)Six studies of medullary thyroid cancer reported test performance data on between 1 and 6 subjects. A total of 17 subjects were included.

Data on relatively rare tumor types that may have variable secretion of tumor markers (eg, Tg) and variable uptake of iodine (for WBS) are sparse. Nine studies reported data on subjects with Hürthle cell tumors (49 subjects in seven studies), poorly differentiated tumors (28 subjects in one study), anaplastic tumors (6 subjects in two studies), eosinophilic tumors (4 subjects in one study), and tall cell papillary cancer (1 subject).

Only two studies, Grunwald (1999) and Helal (2001), reported on at least 10 subjects with and 10 without metastatic disease, the minimum number of subjects needed to provide minimally reliable estimates of both sensitivity and specificity. Grunwald (1999) is the larger study and the only study with a large number of subjects without metastatic disease, but it suffers from being a retrospective study that apparently combined previously reported patients from multiple centers, not having a predetermined definition of a reference standard (whether subjects actually have metastatic disease or not), not blinding PET interpreters from clinical data, and not focusing on subjects with elevated Tg and negative WBS. The sample of subjects is therefore likely to be heterogeneous and the applicability of the findings may be questionable. While the study appears to be multicenter, no analysis is reported accounting for possible differences among centers or PET scanners. The evaluation of subjects with marker of disease, but no other evidence of metastasis, is only a

sub-group analysis of the whole data set. This subgroup also is incompletely defined. All subjects had Tg levels greater than 5 ng/mL, although it is unclear whether this threshold was based on suppressed or non-suppressed conditions. Helal (2001) was of better quality, being a prospective, blinded study with predetermined reference standards and PET interpreter blinding that focused on subjects with treated differentiated thyroid cancer, elevated Tg and negative WBS. While the subjects were consecutively submitted to PET evaluation at one center, it is unclear if the subjects represented a selected sample of subjects who had their primary treatment at various hospitals. The study is relatively small and was barely of sufficient size to give a reliable estimate of specificity (with only 11 subjects without metastatic disease).

The remaining smaller, generally retrospective studies, that did not always have clear reference standards or reporting, found PET sensitivity that ranged from 62% to 100% but specificity that varied over the full range (0% to 100%). For the studies that we were able to combine using the random effects model, including the two larger studies, we found a combined sensitivity of 84% (95% confidence interval 73%-91%) and a pooled specificity of 56% (95% confidence interval 27%-82%). However, given the wide variability of test performance across studies and the extremely small number of subjects

without metastatic disease group in some studies, these combined estimates are not reliable and are of questionable value.

Only one study provided test performance data for more than a handful of subjects with Hürthle cell tumors. Grunwald (1999) analyzed 20 subjects with Hürthle cell tumors; no data were provided about Tg level; 2 of the subjects had positive WBS. PET sensitivity to diagnose metastatic disease was 87% and specificity was 100%. Besides the small number of subjects and the mixed population, this analysis suffers from the same problems as discussed above for this paper.

The same study also compared PET test performance of subjects with well differentiated and poorly differentiated tumors (using an unvalidated grading system). Test performance for PET was actually somewhat lower for well-differentiated tumors than poorly differentiated tumors. This was thought to be because well-differentiated tumors are slower growing and less metabolically active (therefore, they would take up less FDG).

Data on the test performance of PET for diagnosis of metastatic disease in patients with medullary cancer, elevated calcitonin and negative standard imaging tests are sparse. Among six studies, the largest included only 6 subjects. No study included more than 1 subject without metastatic disease. Three studies had no subjects without metastatic disease. Therefore no

individual study provides any useful information about the test performance of PET for medullary cancer. The ability to make comparisons among studies and to generalize the findings from each study is further limited by the different imaging tests used prior to PET from study to study subject to subject. These imaging tests included CXR, CT, MRI, US and various forms of scintigraphy. No subject was reported to have all tests. Nevertheless, by doing a simple combination of the 17 subjects in these studies, a rough estimate of test performance found sensitivity of 92% and specificity of 50%. However, these values should be treated with skepticism. This method of combining test performance data does not have true validity. Even by broadening the population of interest to all patients with treated medullary cancer and elevated calcitonin, regardless of other imaging test results, the largest study had complete data on only 17 subjects. In contrast to the other much smaller studies, sensitivity was only 76%. All subjects had metastatic disease so specificity could not be calculated. Two patients, however, were excluded because final diagnosis data were not obtained.

Two studies directly compared PET to SRS and DMSA scintigraphy for medullary cancer in 13 subjects. Whereas PET was highly sensitive for localizing metastases, SRS and DMSA scintigraphy were false negative for almost all subjects and lesions.

There were insufficient data in the literature to estimate PET test performance for tumor types other than well-differentiated thyroid cancer, Hürthle cell tumors, or medullary cancer.

Data on false positive PET scans

Nine studies had 33 subjects with false positive PET scans. Fifteen of these subjects had elevated biochemical markers and negative imaging tests. Overall, 60% of false positive lesions were located in the neck. The only clinically important findings by PET among the lesions false positive for cancer were one case of tuberculosis and one case of fibrous dysplasia of the humerus. At least nine subjects had biopsies or surgery that would not have been done based on other imaging tests, that were negative for clinically important diagnoses. However, assessment of the subjects with false positive PET, and calculation of PET test performance, is limited by the fact that only about half the subjects had histology of the reported false positive lesions. It is likely that a number of the subjects whose diagnoses were based on other imaging tests had true positive PET scans that were unconfirmed.

Effect of FDG PET on health outcomes or clinical management of previously treated thyroid cancer suspected to be metastatic for which standard imaging modalities have failed to localize metastatic lesions or are thought not to be helpful to locate metastatic disease

Data on the effect of PET on patient management or clinical outcomes for patients with treated differentiated thyroid cancer, elevated Tg and negative WBS were reported in seven small studies with a total of 97 subjects. Overall, about 80% of subjects with positive PET scans were reported to have further treatment (surgery, radioiodine ablation, or retinoic acid treatment) based on the PET results. About 20% of subjects had no change in treatment based on PET, not including subjects reported only in a letter for whom PET was explicitly ignored for treatment management. In four studies, one-third of subjects had reported cure of metastatic disease from treatment that was based on PET. However, one study had a mean follow-up duration of only 6 months and two studies did not provide data on follow-up duration.

Data on the effect of PET on patient management or clinical outcomes for patients with treated medullary cancer and elevated calcitonin are limited. One study of 8 subjects with negative standard imaging tests reported that 2 of the subjects had curative surgery based on PET. No follow-up duration was reported. The only study of subjects with medullary cancer that included more than 10 subjects evaluated patients regardless of other imaging test results. The study found that 60% of 15 subjects with positive PET had surgery based on PET. No data were reported on cure rate. Thus, no reliable estimates of the

effect of PET on clinical management or outcomes of patients with treated medullary thyroid cancer have been published.

No useful data have been reported on the effect of PET on clinical management or outcomes of patients with other forms of thyroid cancer.

Overall, the published data on test performance and effect on clinical management and outcomes of PET for patients with thyroid cancer, biochemical evidence of metastasis and negative standard imaging tests are sparse and of poor quality. Of 41 published primary articles on PET for diagnosis of metastasis in treated thyroid cancer, only two are sufficiently powered to provide potentially reliable estimates of both sensitivity and specificity for the populations of interest. Both of these studies evaluated patients with differentiated thyroid cancer. No study directly addressed the question of whether the use of PET has an effect on patient management, cure rate and survival. No study reported clear, complete data that could be used to estimate the clinical value of PET for diagnosis of metastatic thyroid cancer.

In conclusion:

- Only two studies reported on at least 10 subjects both with and without metastatic differentiated thyroid cancer who had elevated Tg, and negative WBS. However, poor quality and small sample size limit their reliability
  - A subgroup of 65 subjects in one study found sensitivity = 88% and specificity =100%
  - A second study of 37 subjects found sensitivity = 96% and specificity, based on only 11 subjects, = 73%
  - Nine smaller studies provided unreliable estimates of test performance
    - Sensitivity ranged from 62% to 100%
    - Specificity ranged from 0% to 100%
  - Combined test performance (using a random effects model) of all the studies found sensitivity = 84% (95% confidence interval 73%-91%) and specificity = 56% (95% confidence interval 27%-82%)
    - However, these combined estimates are not similar to any study's findings and are not reliable due to the variability of test performance across studies and the small study sizes
- No study had sufficient subjects to estimate the test performance of PET for patients with treated medullary cancer, elevated calcitonin and negative standard imaging tests to diagnose metastatic disease

    - The largest such study included only 6 subjects
    - A simple summation of subjects across six studies yielded overall sensitivity = 92% and specificity = 50%.
        - These values are at best preliminary estimates and should not be considered to be accurate or reliable.
- Two studies with 13 subjects with medullary cancer directly compared PET to SRS and DMSA scintigraphy. 12 subjects had 62 confirmed positive lesions on PET. Of these, SRS was positive for only one lesion and DMSA scintigraphy was positive for only two lesions in 2 subjects.
- Little data exist on the test performance of PET for patients with rare forms of thyroid cancer to diagnose metastatic disease
    - One study with 20 subjects with Hürthle cell tumors found sensitivity = 87% and specificity = 100%
    - One study with 28 subjects with poorly differentiated tumors found sensitivity = 76% and specificity = 82%
        - Among 39 subjects with well-differentiated tumors, sensitivity = 66% and specificity = 100%
    - Insufficient data exist to estimate test performance for various rare tumor types
- Nine studies reported 33 subjects with false positive PET

    - 60% had false positive lesions in their neck
    - At least 9 subjects had biopsies or surgery based on PET alone that were negative for clinically important disease
    - 1 subject had tuberculosis and 1 had fibrous dysplasia of the humerus discovered based on otherwise false positive PET
- No study was specifically designed to determine the effect of PET on clinical management or outcomes in patients with treated thyroid cancer, and provided quantitative estimates
- Among six small studies of subjects with treated differentiated thyroid cancer, elevated Tg, and negative WBS, about 80% of subjects had treatment for metastatic disease based on positive PET, about 20% of subjects had no change in management, about one-third had short-term (about 6 month to 3 year) reported cure and one-third had tumor recurrence after treatment (the remainder are not described)
- Only two small studies evaluated effect of PET on clinical management or outcomes in patients with treated medullary cancer, elevated calcitonin and negative standard imaging tests. Three of 9 subjects had surgery and reported cure after PET; no data were provided as to duration of cure
- No data were reported on the effect of PET on clinical management or outcomes in patients with rare forms of thyroid cancer

- Overall, studies on the use of PET for thyroid cancer are small and of poor quality.

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Table 1. Search strategies

#	Search History	Results	Description
1	exp thyroid gland/ or thyroid gland.af	41537	Thyroid, Thyroid cancer, and Thyroid cancer markers
2	exp thyroid neoplasms/ or thyroid neoplasm.af	21267	
3	thyro$.af.	187518	
4	(cancer$ or neoplasm$ or tumo$).af.	2090496	
5	exp thyroglobulin/ or thyroglobulin.af	9496	
6	exp calcitonin/ or calcitonin.af.	23125	
7	1 or 2 or (3 and 4) or 5 or 6	102253	
8	(positron or pet or fdg).af.	32688	FDG PET scanning and related diagnostic tests
9	exp fludeoxyglucose f 18/ or fludeoxyglucose.af.	3686	
10	exp radionuclide imaging/ or radionuclide imaging.af.	57655	
11	exp diagnostic techniques, radioisotope/	132768	
12	exp tomography, emission-computed/	27411	
13	(spect or single photon emission).af.	20192	
14	(63503-12-8 or 154-17-6).rn.	11366	
15	8 or 9 or 10 or 11 or 12 or 13 or 14	170618	
16	7 and 15	4461	PET and Thyroid
17	Limit 16 to English language	3276	
18	Limit 17 to human	2408	
19	Limit 18 to yr=1980-2001	**1392**	

Table 2. Studies evaluating PET for previously treated thyroid cancer
Part I

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Adams, 1998 EJNM	Location: Germany Specialty: Nuclear medicine, Internal medicine Mean age (Range): 49 (34-59) y Female: 50% Race: ND Enrolled: 8 Evaluated: 8 Number of sites: ND Study period: ND	Medullary thyroid carcinoma Prior thyroidectomy and repeated cervical lymph node dissection Elevated calcitonin (all > 850 ng/mL) and elevated CEA (all > 20 ng/mL) Indeterminate findings on radiography, US, or CT.	ND	Prior total thyroidectomy more than 4 y previously, and also prior repeated cervical lymph node dissection. FDG PET performed after > 12 hr fast. 374 FDG 60 min pre-scan. Whole-body scan performed in 3-5 bed positions 12-15 min/position with a regional scan on thorax or abdomen. Scans read by two nuclear physicians and radiologists without knowledge of patient background	Prospective
Adams, 1998 NMC	Location: Germany Specialty: Nuclear medicine, Internal medicine Mean age (Range): 39 (24-59) y Female: 60% Race: ND Enrolled: 5 Evaluated: 5 Number of sites: ND Study period: ND	Medullary thyroid carcinoma Prior thyroidectomy and repeated cervical lymph node dissection Elevated calcitonin (all > 2385 ng/mL) and elevated CEA (all > 5 ng/mL)	Patients with known diabetes mellitus	Prior total thyroidectomy more than 4 y previously, and also prior repeated cervical lymph node dissection. FDG PET performed after > 12 hr fast. 374 FDG 60 min pre-scan. Whole-body scan performed in 3-5 bed positions 12-15 min/position ND on scan interpretation or blinding.	Prospective

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Alnafisi, 2000	Location: Canada Specialty: Diagnostic radiology, Nuclear medicine, Pathology Mean age (Range): 41 (19-66) y Female: 82% Race: ND Enrolled: 11 Evaluated: 11 Number of sites: ND Study period: ND	Differentiated (papillary) thyroid cancer Prior thyroidectomy and ablation. Negative WBS and elevated Tg (all > 25 ng/mL , non-suppressed)	ND	All but one patient received full thyroid hormone when PET performed. FDG PET performed 40 min after 185 MBq FDG in fasting patients. Data were obtained in 15 cm sections with an acquisition time of 8 min. Total scanning time was about 1 hr. ND on scan interpretation or blinding.	Retrospective
Brandt-Mainz, 1998	Location: Germany Specialty: ND Age: ND Female: 55% Race: ND Enrolled: 20 Evaluated: 20 Number of sites: ND Study period: ND	Differentiated thyroid cancer Prior thyroidectomy and ablation. Negative WBS and elevated Tg (> 1.0 ng/mL, N=14), or Markedly elevated Tg (> 10 ng/mL) and “inadequate” tumor mass (N=4), or Positive US and normal Tg (N=2)	ND	Prior thyroidectomy, radioiodine ablation of the thyroid remnant, and suppressive levothyroxine replacement therapy. FDG PET performed after overnight fast. 350 MBq FDG 30 min pre-scan. Scan performed on the neck and chest. Scans read independently by two experienced observers blinded to the clinical data.	Prospective
Brandt-Mainz, 2000	Location: Germany Specialty: ND Age: ND Female: 65% Race: ND Enrolled: 20 Evaluated: 18 Number of sites: ND Study period: ND	Medullary thyroid carcinoma Prior thyroidectomy	Diabetes mellitus Unable to validate diagnosis	Prior total thyroidectomy in all patients; some with lymph node resection. FDG PET performed after overnight fast. 350 MBq FDG 30 min pre-scan. Scan performed from the neck and chest in 6 bed positions. Scans read independently by two experienced observers blinded to clinical data.	?Retrospective (“Performed PET in patients”)

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Chung, 1999 [Yeo, 2001, overlapping set: data in brackets]	Location: South Korea Specialty: Nuclear medicine, Internal medicine, Surgery Mean age (Range): 48 (24-72) y Female: 78% Race: (Korean) Enrolled: 54 [37] Evaluated: 54 [22] Number of sites: 1 Study period: 1995-1997 [1995-1999]	Thyroid cancer Prior thyroidectomy and ablation. Negative WBS and suspected of having metastasis Papillary cancer (not explicitly stated in methods) [FDG positive in cervical lymph nodes]	ND	All subjects had prior thyroidectomy and subsequent radio-ablation therapy. PET scan performed under thyroxine replacement therapy, patient fasting, 370-555 Mbq FDG IV 60 min before scanning. Interpretation made by consensus of 2 nuclear physicians. Scans read by two experienced nuclear physicians, who reached a consensus. ND on blinding.	?Retrospective (unclear)
Conti, 1999	Location: USA Specialty: Radiology and medicine Age: ND Female: ND Race: ND Enrolled: 30 Evaluated: 30 Number of sites: 1 Study period: ND Period of follow-up: 3 y	History of thyroid cancer Prior thyroidectomy and ablation. Suspected recurrent papillary and/or follicular thyroid carcinoma Differentiated cancer: negative WBS and elevated (“about 8 ng/mL”)or rising Tg (ND) or detectable anti-Tg antibodies (ND) Medullary cancer: elevated or rising calcitonin	ND	Prior surgical and ^{131}I thyroid ablation with levothyroxine suppression. FDG PET performed delayed images of the neck, chest, abdomen, and pelvis in the fasting state. 10 mCi FDG 40-45 min pre-scan. Other imaging modalities within 1 year, including Thallium, MIBI, CT, MRI, and US were retrospectively compared with PET. Surgical, laboratory, and/or therapy outcome data within the follow-up period was obtained. Scans read independently by two expert readers and by consensus. ND on blinding.	Unclear (“Referred to PET center”)

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Frilling, 2000	Location: Germany Specialty: General or transplant surgery, Nuclear medicine Mean age (Range): 43 (35-73) y Female: 31% Race: ND Enrolled: 13 Evaluated: 13 Number of sites: 2 Study period: 1992-1999	Differentiated thyroid carcinoma Prior thyroidectomy and ablation. Suspected disease recurrent (6 months after surgery) to regional lymph nodes or thyroid bed, or both Negative WBS and elevated Tg levels (> 10 ng/mL, non-suppressed), or WBS result was discordant with US result.	ND	Initial thyroidectomy treatment and prior cervical US. FDG PET performed after an overnight fast. 400 MBq FDG 60 min pre-scan. Scan performed from 7-8 bed positions; axial field of view: 15.2 cm. "Two experienced teams from the Department of Nuclear Medicine reviewed the results of all preoperative diagnostic methods." ND on blinding.	Prospective cohort
Gasparoni, 1997	Location: Italy Specialty: Nuclear medicine, Endocrinology Mean age (Range): 50 (44-66) y Female: 80% Race: ND Enrolled: 5 Evaluated: 5 Number of sites: ND Study period: ND	Medullary thyroid carcinoma Preoperative (N=3) or Prior thyroidectomy and lymphoadenectomy (N=2) Elevated calcitonin (all > 30 ng/L) and elevated CEA (all > 5 ng/mL) either pre- or postoperatively	ND	Preoperatively for staging or after thyroidectomy and lymphoadenectomy. FDG PET performed after an overnight fast, by injecting 370-444 MBq FDG. Scans read by three authors without knowledge of clinical or radiologic findings. For discordant cases, diagnosis reached by consensus.	Retrospective

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Grunwald, 1997	Location: Germany Specialty: Nuclear medicine Age: ND Female: 78% Race: ND Enrolled: 54 Evaluated: 54 Number of sites: ND Study period: ND	Differentiated thyroid cancer Prior thyroidectomy and ablation	ND	FDG PET performed when no major masses of benign remnant tissue were expected. FDG PET performed after > 16 hr fast. 200-400 MBq FDG 45 min pre-scan. Scan performed in 4-5 bed positions from the base of the skull. ND on scan interpretation or blinding.	Retrospective
Grunwald, 1999	Location: Germany Specialty: Nuclear medicine Age: ND Female: 68% Race: ND Enrolled: 222 Evaluated: 222 Number of sites: ?7 Study period: ND	Differentiated thyroid cancer Prior thyroidectomy and ablation	ND	PET scan after thyroidectomy and a mean of 3-4 preceding treatments with ^{131}I (at which point no major masses of benign remnant tissue were expected). Patient fasting. 200-400 MBq FDG IV at least 30 min before static imaging. ND on scan interpretation or blinding.	Retrospective
Helal, 2001	Location: France Specialty: Nuclear medicine Mean age (Range): 50 (27-78) y Female: 49% Race: ND Enrolled: 37 Evaluated: 37 Number of sites: 1 Study period: ND	Differentiated thyroid carcinoma Prior thyroidectomy and ablation Negative WBS and elevated Tg (> 1 ng/mL under TSH suppression, or >10 ng/mL under TSH stimulation)	(No patient had positive Tg antibody tests)	Underwent total thyroidectomy and ^{131}I ablation therapy. Prior lymph node dissection and 1-6 therapeutic doses of ^{131}I during follow-up. FDG PET performed after 12 hr fast. 370 MBq FDG 50-60 min pre-scan. Scans read independently by two experienced physicians blinded to the clinical data. Disagreements resolved by consensus.	Prospective cohort

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Lind, 2000	Location: Austria Specialty: Nuclear medicine, Endocrinology Age range: 24-89 y Female: 65% Race: ND Enrolled: 60 Evaluated: 60 Number of sites: 1 Study period: ND	Thyroid cancer (Prior thyroidectomy and ablation, implied) If differentiated tumor: elevated Tg (ND on definition), negative WBS or faint WBS uptake and markedly elevated Tg (ND). If medullary tumor: elevated calcitonin All anaplastic tumors	ND	PET scan after therapy for thyroid cancer and biomarker and WBS work-up for metastases as appropriate. ND on scan interpretation or blinding.	Retrospective
Muros, 2000	Location: Spain Specialty: Nuclear medicine, Surgery Mean age (Range): 37 (19-72) y Female: 70% Race: ND Enrolled: 10 Evaluated: 10 Number of sites: 1 Study period: ND Period of follow-up: 3-6 y	Differentiated thyroid carcinoma Prior thyroidectomy and ablation Negative WBS and elevated Tg (ND on definition)	ND	Prior total thyroidectomy. FDG PET performed after at least 6 hr fast and muscle repose. 5 MBq of FDG per kg body weight 45 min pre-scan. Whole-body images and cross-sections were obtained. ND on scan interpretation or blinding.	?Prospective (poor description, informed consent obtained)
Musholt, 1997	Location: Germany Specialty: Surgery Mean age (Range): 36 (11-52) y Female: 30% Race: ND Enrolled: 10 Evaluated: 10 Number of sites: ND Study period: Jan. – Dec. 1996	Medullary thyroid carcinoma Prior operative treatment Elevated calcitonin (all > 0.27 ng/mL)	ND	Prior operative treatment. 10-15 mCi FDG 40 min pre-scan. ND on scan interpretation or blinding.	“Consecutively treated”

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Simon, 1996	Location: Germany Specialty: Nuclear medicine, Diagnostic radiology, Radiological Science Case age: 64 Case gender: Female Race: ND Enrolled: 1 Evaluated: 1 Number of sites: 1 Study period: ND	Medullary thyroid carcinoma Subtotal thyroidectomy and neck dissection Elevated calcitonin (5.70 ng/mL), and inconclusive other imaging finding, including US, CT and radiograph.	N/A	Subtotal thyroidectomy and left-sided neck dissection 4 months prior. FDG PET performed 90 min after FDG injection. ND on scan interpretation or blinding.	Single case report
Stokkel, 1999	Location: Netherlands Specialty: Nuclear medicine, Endocrinology Mean age (Range): 47 (26-73) y Female: 55% Race: ND Enrolled: 11 Evaluated: 11 Number of sites: ND Study period: ND Mean period of follow-up: 15 (13-19) months	Differentiated papillary thyroid cancer Suspicion of tumor recurrence, based on a detectable serum Tg concentration. Prior thyroidectomy and ablation. Detectable Tg (all > 4 ng/mL, nonsuppressed)	(No patient had positive Tg antibody tests)	Prior total thyroidectomy and radioiodine ablation. FDG PET performed after 6 hr fast. 186 MBq FDG 60 min pre-scan. Scan included head and neck, chest, and abdomen. For patients with negative WBS and positive PET, post US and/or CT or MRI were performed. Scans read on the basis of consensus between two experienced nuclear medicine physicians. ND on blinding.	Unclear ("Patients… were studied")
van Tol, 2000 Letter	Location: Netherlands Specialty: Endocrinology, Nuclear medicine Mean age (Range): 57 (26-75) y Female: 73% Race: ND Enrolled: 11 Evaluated: 11 Number of sites: ND Study period: ND	Differentiated thyroid carcinoma Prior thyroidectomy and ablation Negative WBS and elevated Tg (>1.5 ng/mL)	ND	Prior total thyroidectomy and ^{131}I ablation therapy. Procedure of FDG PET not reported. ND on scan interpretation or blinding.	"Consecutive series"

Table 2, Part I, continued

Author, Year	Demographics	Inclusion Criteria	Exclusion Criteria	Procedures	Study Design
Wang, 2000 [Wang 1999, subset: data in brackets]	Location: Germany Specialty: Nuclear medicine, endocrinology, Radiology, Medical physics, Pathology Mean age (Range): ND [47 (13-76) y] Female: ND [62%] Race: ND Enrolled: 125 [37] Evaluated: 125 [37] Number of sites: ND Study period: Nov. 1995 – March 1999 [1995-1998]	Differentiated thyroid cancer Negative WBS with elevated Tg (ND or definition or n), or High risk patients (> 45 y,poorly differentiated tumor, tumor extension, > 4 cm) and known distant metastases by other imaging modalities.	ND	Total thyroidectomy (N=92), subtotal thyroidectomy (N=13), hemithyroidectomy (N=17), no surgery (N=3). Ablation (N=101) FDG PET performed under both high TSH (N=65) and low TSH (N=60). FDG PET performed after 6 hr fast.370 MBq FDG IV 45-60 min pre-scan. Scan performed from maxilla to at least the level of the umbilicus. ND on scan interpretation or blinding.	?Retrospective (unclear)

Table 2.
Part II

Author, Year	Tumor Type (N)	Definition of PET Positive	Reference Standard
Adams, 1998 EJNM	Medullary 8	Increased FDG uptake	Surgery or long-term follow-up (> 1 year).
Adams, 1998 NMC	Medullary 5	Increased FDG uptake	Surgery or long-term follow-up (> 1 year).
Alnafisi, 2000	Differentiated tumor 11 Papillary 7 Tall cell variant of papillary 1 Follicular 3	FDG localization	US and CT, including guided FNA of any accessible lesions. Reviewed pathology reports. Pathologist reviewed the original specimens that could be retrieved to determine unusual histological features.
Brandt-Mainz, 1998	Differentiated tumor 20 Papillary 15 Follicular 1 "Eosinophilic" 4	ND	Clinical surgery and/or CT with a high-resolution technique of the neck and the chest.
Brandt-Mainz, 2000	Medullary 18	ND	Surgery/histology (N=11); CT, MRI or venous catheterization (N=5); ND (N=2)
Chung, 1999 [Yeo, 2001, overlapping set: data in brackets]	Differentiated tumor 54 Papillary 54 [Differentiated tumor 22 Papillary 22]	Lesion had SUV of > 3.0 or FDG uptake had increased abnormally and was higher than in surrounding normal tissue [Same]	Cervical lymph node dissection (N=11) [(N=22)] Mediastonoscopic biopsy (N=1) Clinically by CXR, US, CT or MRI. Overall clinical evaluation made including pathological findings, US, CT, MRI and appraisal of subsequent clinical course.
Conti, 1999	Differentiated tumor 24 Papillary or Follicular Medullary 6	Lesion	Prior other imaging and surgical findings; and, follow-up clinical course.
Frilling, 2000	Differentiated tumor 13 Papillary 7 Follicular 5 Hürthle cell 1	Pathologic uptake	Histology
Gasparoni, 1997	Medullary 2 (postoperative) Sporadic 2	SUV > 2.5	Laparotomy

Table 2, Part II, continued

Author, Year	Tumor Type (N)	Definition of PET Positive	Reference Standard
Grunwald, 1997	Differentiated tumor 54 Papillary 39 Follicular 15	Radiopharmaceutical uptake by at least one tumor site	Overall clinical evaluation, including histology, cytology, Tg level , US, CT, MRI, and subsequent clinical course.
Grunwald, 1999	Differentiated tumor 222 Papillary 134 Follicular 80 Mixed-cell type 8 (Hürthle cell 20)	At least one site showed radiopharmaceutical uptake	Clinical evaluation, including histology, cytology, Tg level, US, CT, and subsequent clinical course
Helal, 2001	Differentiated tumor 37 Papillary 26 Follicular 11 (Hürthle cell 4)	Focal uptake relatively higher than that of surrounding tissue with no similar activity seen in the contralateral side of the body.	Histopathology confirmed by biopsy or surgery findings. Follow-up observations for patients with negative PET or presumed false-positive PET.
Lind, 2000	Differentiated tumor 48 Papillary 18 Papillary oxyphilic subtype 2 Follicular 23 Follicular oxyphilic subtype 5 Medullary carcinoma 8 Anaplastic tumor 4	ND	ND
Muros, 2000	Differentiated tumor 10 Papillary 7 Follicular 2 Follicular-papillary 1	Abnormal focal localization of the radiopharmaceuticals in a pattern consistent with residual or metastatic disease.	Clinical, radiological, or pathological findings.
Musholt, 1997	Medullary 8 Sporadic 2 MEN IIA 6	Foci of abnormal radiotracer accumulation	Intraoperative and histopathologic exams.
Simon, 1996	Medullary 1	Sharply demarcated focus of increased FDG uptake	Histologic examination of the residual thyroid specimen
Stokkel, 1999	Differentiated tumor 11 Papillary 11	Focus of increased uptake	Positive PET: FNA Negative PET: Clinical follow-up for 13-19 months
van Tol, 2000	Differentiated tumor 11 Papillary 6 Follicular 3 Hürthle cell 2	Abnormal FDG uptake	Biopsy or surgery (N=3) CT, MRI, CXR; and follow-up observation (17-38 months, N=8)

Table 2, Part II, continued

Author, Year	Tumor Type (N)	Definition of PET Positive	Reference Standard
Wang, 2000 [Wang 1999, subset: data in brackets]	Differentiated tumor 123 [37] Papillary 93 [30] Follicular 18 [5] Hürthle cell 12 [2] Anaplastic 2	FDG uptake [Focus of increased FDG uptake greater than normal mediastinal activity and SUV > 3]	Death [Imaging, serology, biopsies]

Table 2.
Part III

Author, Year	Results	Comments	FP/FN PET
Adams, 1998 EJNM	**For subjects with medullary cancer, negative imaging tests, and elevated calcitonin (all > 850 ng/mL) and elevated CEA (all > 20 ng/mL, N=6), FDG PET sensitivity was 100% (N=5) to diagnose metastatic disease; there was 1 TN subject.** For subjects with medullary cancer and negative CXR, US and CT and elevated calcitonin and CEA (N=8), sensitivity was 100% (N=7); there was 1 TN subject. 1 subject with 9 lesions found on PET had one found by DMSA. 1 subject with 10 lesions found on PET had 1 found on both DMSA and SRS. 2 subjects had surgery for recurrent medullary cancer based on PET (and possibly DMSA and SRS -- text unclear).	Incomplete data reported on subject with negative PET. No data on funding source. Other negative / indeterminate imaging included: DMSA scintigraphy, SRS, CXR, abdominal and neck US, neck and chest CT	FP = 0 FN = 0
Adams, 1998 NMC	**For subjects with medullary thyroid cancer, negative CT, and elevated calcitonin (all > 4500 ng/mL) and elevated CEA (all > 58 ng/mL, N=2), both had TP results on FDG PET to diagnose metastatic disease.** **Both patients had surgical removal of tumor-involved head and neck LN; 1 subject had progression of disease at 1 year.** For subjects with medullary cancer and elevated calcitonin and CEA (N=5), FDG PET sensitivity was 100% (N=5) to diagnose metastatic disease. All patients had surgical removal of tumor-involved head and neck LN; 2 subjects had progression of disease at 1 year.	No data on funding source. Other negative imaging included: SRS, Thoracic CT. Abdominal and neck US and CXR were performed, but results were not reported.	FP = 0 FN = 0

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Alnafisi, 2000	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 25 ng/mL non-supressed, N=11), FDG PET sensitivity was 86% (N=7) and specificity was 0% (N=4) after initial PET scan.** The one patient with a negative PET had a second PET 16 months later due to rising Tg, which was positive. **Positive PET resulted in treatment or further evaluation in all 11 (including subsequently positive PET): 9 had fine needle aspiration, all had US, 6 had surgery and/or radioiodine ablation, with confirmed resolution (by PET, US, or CT) 5; ND on 1. 1 subject refused surgery. 4 with FN PET continue disease-free under observation.**	No imaging follow-up for patients with negative PET results. No data on funding source.	FP = 4: 1 with normal CT, US; 1 discordant with CT, normal US; 2 with concordant CT and US and benign or non-diagnostic biopsy. All stable clinically (ND duration); 2 thyroid, 1 thyroid/neck, 1 neck FN = 1: Follow-up PET was positive; submandibular LN
Brandt-Mainz, 1998	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 1 ng/mL, N=14), FDG PET sensitivity was 61% (N=13); there was 1 subject with a true negative scan.** For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 1 ng/mL, N=14) or highly elevated Tg (> 10 ng/mL) and only small mediastinal foci on WBS, FDG PET sensitivity was 72% (N=16) and specificity was 100% (N=2).	No data on funding source.	FP = 0 FN = 5: 2 found by CT, ND on how 3 found. 1 with negative CT; all with negative US; 1 lung, 1 mediastinum/lung, 3 ND
Brandt-Mainz, 2000	**For subjects with medullary thyroid cancer and elevated calcitonin (>50 ng/L) and elevated CEA (>2 ng/mL, N=17), sensitivity was 76% (N=17). Specificity could not be calculated as all subjects had metastatic disease.** Two subjects with positive PET were excluded because surgical confirmation had not been performed. One subject with normal calcitonin and CEA had a true negative scan.	Two patients with unverified positive PET were excluded from the sensitivity and specificity calculation. No data on funding source.	FP = 0 FN = 4: 1 found by US and positive histology; 1 found by selective venous catheterization and positive histology; 2 could not be localized by other imaging modalities (ND on diagnostic method); 2 neck LN, 2 ND

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Chung, 1999 [Yeo, 2001, overlapping set: data in brackets]	**For subjects with papillary thyroid cancer, negative WBS and elevated Tg (> 10 ng/mL on TSH stimulation or > 1.0 ng/mL on TSH suppression, N=23), FDG PETsensitivity was 94% (N=18) and specificity was either 80% or 100% (N=4 or 5) to diagnose metastatic thyroid cancer;** unclear if one patient with false positive PET had elevated or normal Tg). For all subjects with negative WBS (N=55), sensitivity was 94% (N=33) and specificity was 95% (N=21). For subjects with negative WBS and normal Tg (N=31), sensitivity was 93% (N=15) and specificity was 94% or 100% (N=16) Eleven subjects had cervical lymph node dissection based on PET. All but one had either elevated Tg or anti-Tg antibody (the other subject had normal Tg, but no anti-Tg antibody titer drawn). All had positive pathology. [Among 96 patients with differentiated thyroid cancer who were suspected of having metastases and had negative WBS, 37 had FDG uptake in cervical lymph nodes. Of these 22 had surgery. For the dissected lymph node groups (N=85), sensitivity was 80% (N=56) and specificity was 83% (N=29).]	Data on test performance for subgroups divided by presence of anti-Tg antibody and of location of metastatic sites found by PET in both those with negative WBS and a comparison group of subjects with positive WBS. [At least 8 subjects in Yeo, 2001 included in Chung, 1999]	FP = 1: Patient with tuberculosis; mediastinum FN = 2: No data
Conti, 1999	For subjects with medullary cancer, negative other imaging and elevated calcitonin (>100 ng/mL, N=2), both had positive PET; 1 had positive surgical confirmation of metastasis (and negative MRI and octreoscan); 1 did not receive treatment during 2 year follow-up For subjects with medullary cancer and elevated calcitonin (>100 ng/mL, N=6), all had positive PET; 2 had positive surgical confirmation of metastasis; 2 had concordant CT; and 2 had no other diagnostic data.	No true reference standard. Included only because of dearth of information on medullary cancer Many patients were lost to follow up. No data on funding source. No test performance data could be calculated. Other negative imaging includes (for MTC subjects): Subject S.B. MRI, Octreoscan; Subject L.J. CT, Octreoscan	Data available only on follow-up disposition (treated, non-treated, and biochemical marker levels)

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Frilling, 2000	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 10 ng/mL, non-suppressed, N=11), FDG PET sensitivity was 82% (N=9) to diagnose metastatic thyroid cancer.** All subjects had metastatic disease, so specificity could not be calculated. For subjects with negative WBS and either elevated Tg or inconsistent WBS with US result (N=13), sensitivity was 85% (N=11).	No data on funding source.	FP = 0 FN = 2: Positive US and biopsy; ND location
Gasparoni, 1997	**For subjects with medullary cancer, elevated calcitonin (>30 ng/L) and elevated CEA (> 5 ng/mL), and negative radiological imaging (N=2), 1 subject had a true positive test (sporadic disease, calcitonin levels normalized after surgery) and 1 subject had a false negative test (sporadic disease or MEN IIa, text and table disagree, micrometastases removed on laparotomy).**	Text and Table disagree with each other as to which subject had the false negative PET No data on funding source. Other negative imaging included: US, CT, MRI, MIBI, MDP	FP = 0 FN = 1: micrometastases found on laparotomy; other imaging negative; liver
Grunwald, 1997	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 1 ng/mL, N>12), FDG PET sensitivity was 78% (N=9) to diagnose metastatic thyroid cancer. 2 subjects had false positive scans and at least 1 subject had a true negative scan.** No data are provided on the number of subjects with negative PET, MIBI and tumor tissue (true negative). For subjects with differentiated thyroid cancer, positive or negative WBS and any Tg (N=54, tumor sites = 66), FDG PET sensitivity was 73% (N=30 sites) and specificity was 86% (N=36 sites) to diagnose metastatic cancer sites. See comments for caveats.	Data provided for tumor sites, not patients. Number of true negatives may be overstated and number of false negatives may be understated (sensitivity and specificity may be overstated) due to lack of clarity of reporting. No data on funding source.	FP = 2: 1 with FP MIBI also; both with negative histology (implied); 1 thyroid site, 3 LN sites, 1 distant site FN = 7-8: 2 with negative WBS, 5 with positive WBS; 3 with negative MIBI, 2 with positive MIBI; 1 with Tg $\leq$ 1 ng/mL, 6 with Tg 2->10,000 ng/mL; all with positive histology (implied) Incomplete data; 1 thyroid site, 4 LN sites, 3 distant sites

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Grunwald, 1999	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (≥ 5 ng/mL, N=65), FDG PET sensitivity was 88% (N=40) and specificity was 100% (N=25) to diagnose residual thyroid cancer.** For all subjects (N=222), sensitivity was 75% (N=109), specificity was 90% (N=113). For subjects with negative WBS (N=166), sensitivity was 85% (N=55), specificity was 90% (N=111). For subjects with negative WBS and normal Tg (N=96), sensitivity was 82% (N=11) and specificity was 87% (N=85). For subjects with elevated Tg (≥ 5 ng/mL, N=107), sensitivity was 76% (N=82), specificity was 100% (N=25). For subjects with papillary tumor and negative WBS (N=106), sensitivity was 86% (N=28), specificity was 86% (N=78). For subjects with follicular tumor and negative WBS (N=52), sensitivity was 87% (N=23), specificity was 100% (N=29). For subjects with Hürthle cell tumor and negative WBS (N=18), sensitivity was 92% (N=13), specificity was 100% (N=5). For subjects with well-differentiated tumor (G1 or G1-2) and negative WBS (N=31), sensitivity was 86% (N=7) and specificity was 100% (N=24). For subjects with poorly-differentiated tumor (≥ G2) and negative WBS (N=20), sensitivity was 67% (N=9) and specificity was 82% (N=11). (For all subjects, WBS sensitivity was 50% and specificity was 99%.)	No data on health outcomes. Likely that this report includes patients from other Grunwald studies No data on funding source.	FP =11: all with negative WBS; all with Tg < 5 ng/mL; all papillary; ND on sites FN = 27: 8 with negative WBS (2 with Tg < 5 ng/mL, 5 with Tg ≥ 5 ng/mL, 1 with ND on Tg), 19 with positive WBS (3 with Tg < 5 ng/mL, 15 with Tg ≥ 5 ng/mL, 1 with ND on Tg); 15 papillary, 11 follicular (2 Hürthle cell), 1 ND on tumor type; ND on sites
Helal, 2001	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (≥ 1 ng/mL, N=37), FDG PET sensitivity was 96% (N=26) and specificity was 73% (N=11) to diagnose residual thyroid cancer.** **PET findings led to a change in the management of 29 subjects (78%)**	No data on funding source.	FP = 3: all inflamed cervical LN FN = 1: Cervical LN metastasis seen on US, confirmed at surgery.

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Lind, 2000	**For subjects with differentiated tumor, negative WBS and elevated Tg (not defined, N=48), FDG PET detected malignant recurrence or distant metastases in 97% of cases. "Especially in patients with [a] discrepancy between a clear Tg elevation but only [faint] uptake in the WBS, FDG PET detected additional ^{131}I-negative metastases. In most of those patients FDG PET changed the therapeutic strategy."** In a subgroup of patients with differentiated tumor and completely negative WBS (N=15), all had positive PET. **For subjects with medullary tumor and elevated serum calcitonin (not defined, N=8), FDG PET was "the most sensitive imaging tool compared to morphological methods and [technichium scan or Octreoscan] in detecting lymph node… or distant metastases." In 2 patients, PET led to curative lymph node resection. The remaining 6 patients already had distant metastases.** **For subjects with anaplastic tumor (N=4), "the extent of the disease was demonstrated much better by FDG PET than by other diagnostic procedures." PET did not change therapeutic strategy in any patient.**	No definitions reported on thresholds for biomarkers, definition of positive PET or how final diagnosis made. No clear test performance or health outcome data. Includes all subjects from Lind, 1999. No data on funding source.	ND
Muros, 2000	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (ND, N=10), FDG PET sensitivity was 100% (N=6) and specificity was 25% (N=4) to diagnose metastatic thyroid cancer.** **Positive PET resulted in surgery for 4 subjects.**	Only 4 subjects had surgical confirmation. Follow-up data on subjects with negative PET not reported. Clinical follow-up ranged from 3 to 6 years. No data on funding source.	FP = 3: 1 had "mild" mediastinal FDG uptake that was related to the thymus; 1 had "mild" cervical spine FDG uptake not confirmed by MRI; 1 had FDG uptake in anterior mediastinum not confirmed by CT or CXR. FN = 0

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Musholt, 1997	**For subjects with medullary thyroid cancer, elevated calcitonin (all > 0.27 ng/mL) and negative CT and/or MRI (N=4), 1 subject had a true positive scan, 1 subject had a true negative scan, 1 subject had a false positive scan, and 1 subject had a scan that was positive for benign tissue (false positive) but was negative for malignant tissue (false negative).** For subjects with medullary thyroid cancer and elevated calcitonin (N=8), sensitivity was 100% (N=6, treating subject with FP and FN as a TP since positive PET may have resulted in surgical exploration and diagnosis) and specificity was 50% (N=2).	Also includes data on 2 subjects with MEN 2b related pheochromocytoma Unclear how to assess subject with 1 FP lesion and 1 FN lesion No data on funding source. Other negative imaging included: CT or MRI	FN/FP = 1: 1 subject with 1 FP and 1 FN lesion found in cervical LN. No TP lesions.
Simon, 1996	**In a case report of a patient with medullary thyroid cancer, elevated calcitonin after surgery (5.7 ng/mL) and negative US, CT, CXR, DMSA, and MIBI had a true positive PET. Subsequent MRI also showed metastases (including some missed by PET). Patient had surgery and remained clinically disease-free.**	Single case report. No data on funding source. Other negative imaging included: Neck US and CT, CXR, DMSA, and MIBG.	FP = 0 FN = 0
Stokkel, 1999	**For subjects with papillary thyroid cancer, negative WBS and elevated Tg (> 4 ng/mL, nonsuppressed, N=10), FDG PET sensitivity was 100% (N=7) and specificity was 100% (N=3) to diagnose metastatic thyroid cancer.** **All subjects with positive PET had FNA.** One subject with a positive WBS and elevated Tg had a concordant PET.	Preliminary results. No data on funding source.	FP = 0 FN = 0
van Tol, 2000	**For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 1.5 ng/mL non-supressed, N=11), FDG PET sensitivity was 100% (N=1 to 5) and specificity was 0% (N=10 to 6) to diagnose metastatic thyroid cancer.** 4 subjects had confirmatory CT, MRI and/or CXR but no evident disease on follow-up for 32-34 months. An additional 4 had negative CT, MRI and/or CXR and no evident disease on follow-up for 17-33 months. 3 had biopsies (1 positive, 2 negative). **Positive PET resulted in surgical biopsies in 3; the 1 with positive biopsy was treated successfully with radioiodine ablation, but had multiple lung metastases 3 years later. Therapy was unchanged in 10 of 11 subjects.**	Letter to the Editor No definition of positive PET. Confirmation of diagnosis made in only 3. No data on funding source.	FP: 2-10, depending on definition of reference standard. All did clinically well for average of 32 months; 1 with + PET at cervical LN and pharynx, 1 with + PET at cervical LN (proven by biopsy) FN = 0

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Wang, 2000 [Wang 1999, subset: data in brackets]	**For subjects with differentiated thyroid cancer and negative WBS (N=71), survival up to 36 months was greater in subjects with negative FDG PET (ND) than positive PET (ND) -- from examination of figure. This analysis was not reported.** For all subjects with differentiated thyroid cancer (N=125), survival up to 36 months was greater in subjects with negative FDG PET (99%, N=66) than in subjects with positive PET (80%, N=59) in univariate analysis (p=0.0001). Survival was significantly longer in subjects with negative PET in univariate analysis (p=0.001) For subjects with positive PET (N=59), survival up to 36 months was greater in subjects with SUV < 10 (88%, N=32) than in subjects with SUV > 10 (67%, N=27) in univariate analysis (p=0.0002) Survival was significantly longer in subjects with lower SUV in univariate analysis (p=0.0002). Excluding the subjects with Hürthle cell tumors (N=?12), did not change the significance level. For all subjects (N=125), survival up to 36 months was greater in subjects with lesion volume < 125 mL [96% (95% CI, 91%-100%), N=106] than in subjects with larger lesions [18% (95% CI, 4%-85%), N=19] in univariate analysis (p=0.0001). Median survival of those with lesions > 125 mL was 19 months (95% CI, 8-34 months); median survival was not reached for those with smaller lesions. *continued*	Survival data only, no direct FDG results. Anaplastic tumors (N=2) considered differentiated No data on funding source. *continued*	ND [FP = 4: 1 with lung granulomatous inflammation also seen on CT, 1 with lung lesion not seen on CT, clinically stable at 1 year; 1 with humerus fibrous dysplasia; 1 with FP at tracheostomy FN = 0]

Table 2, Part III, continued

Author, Year	Results	Comments	FP/FN PET
Wang, 2000 [Wang 1999, subset: data in brackets] *continued*	**[For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (> 2 ng/mL with TSH suppression or > 5 ng/mL when TSH was elevated, N=18), FDG PET sensitivity was 71% (N=17); there was 1 FP subject.]** **[or subjects with differentiated thyroid cancer, negative WBS and either elevated Tg or elevated anti-Tg antibody (> 1 ng/dL, N=23), FDG PET sensitivity was 72% (N=18) and specificity was 20% (N=5).]** [For all subjects with negative WBS (N=37), sensitivity was 70% (N=20) and specificity was 76% (N=17).] [For subjects with negative WBS and normal Tg (N=19), sensitivity was 67% (N=3) and specificity was 81% (N=16).] **[For subjects with differentiated thyroid cancer, negative WBS and elevated Tg (N=18),** **11 had further treatment based on PET results:** **10 had true positive PET resulting in treatment (after treatment, 1 had no evident disease, 2 had limited disease and 7 had diffuse disease);** **1 had false positive PET, resulting in biopsy and therapeutic WBS (patient had no evident disease, but continued to have elevated Tg).** **3 had further treatment based on other testing, all with false negative PET:** **1 had biopsy based on ultrasound; 1 had surgery based on ultrasound.** **4 with metastases had no further treatment:** **2 had true positive PET (1 with diffuse disease, 1 with limited disease);** **2 had false negative PET (both with limited disease).]**	[Authors claim that PET had an impact on patient management in 19 patients; however, 3 of these had further interventions based on other tests. Furthermore, 4 patients had further interventions because of false positive PET.]	

Table 3. Test performance of PET for metastatic differentiated thyroid cancer Elevated Tg and Negative WBS (N ≥ 10)

Study	TP (n)	FN (n)	TN (n)	FP (n)	Sensitivity (%)	Specificity (%)	Prevalence of Metastatic Thyroid Cancer (%)
Grunwald, 1999 [a]	35	5	25	0	88	100	62
Helal, 2001	25	1	8	3	96	73	70
Chung, 1999	17	1	4	0-1 [b]	94	80 or 100 [b]	78-82 [b]
Wang, 1999 [c, d]	12	5	0	1	71	[0]	94
Wang, 1999 [c,e]	13	5	1	4	72	20	78
Brandt-Mainz, 1998	8	5	1	0	62	[100]	93
Grunwald, 1997 [a]	7	2	≥ 1 [f]	2	78	≥ 33 [f]	≤ 75 [f]
Alnafisi, 2000	6 [g]	1 [g]	0	4	86 [g]	0	64
van Tol, 2000 [h]	1-5 [i]	0	0	10-6 [i]	100	0	9-45 [i]
Frilling, 2000	9	2	0	0	82	--	100
Muros, 2000	6	0	1	3	100	25	60
Stokkel, 1999	7	0	3	0	100	100	70

TP = true positive; FN = false negative; TN = true negative; FP = false positive; n = number of subjects.
Studies in bold have at least 10 subjects in each group with and without metastatic disease
Sensitivity or specificity results in brackets are based on only one subject.

[a] Subjects from Grunwald, 1997 might also be included in Grunwald, 1999

[b] Unclear if single false positive had elevated Tg.

[c] Included in Table 1 under Wang, 2000.

[d] Only subjects with elevated Tg.

[e] Subjects with either elevated Tg or anti-Tg antibody.

[f] No data reported on subjects with negative PET, MIBI and tissue.

[g] On initial PET. One subject with FN scan had subsequent positive PET (done because of rising Tg).

[h] Letter to the Editor

[i] 4 subjects had CT, MRI and/or CXR concordant with PET but no apparent disease on follow-up for 17-33 months.

Table 4. Change in clinical management of differentiated thyroid cancer directed by PET Elevated Tg and Negative WBS (N ≥ 10)

Study, Year	**N**	**Positive PET** (n)	**Biopsy** (n [%])	**Surgery** (n [%])	**Radioiodine Ablation** (n [%])	**Cure** (n [%])	**Recurrence** (n [%])	**No Change** (n [%])
Lind, 2000	48	ND	Change in therapeutic strategy in "most" subjects			ND	ND	ND
Helal, 2001 [a]	37	28	4 [14] [b]	23 [79] [c]	5 [17] [d]	14 [48] [e]	ND	1 [3]
Wang, 1999 [f]	18	13	ND	4 [31] [g]	10 [77] [g, h]	2 [15] [i,j]	11 [85] [i,k]	2 [15] [L]
Alnafisi, 2000	11	11	9 [82]	4 [36] [m]	5 [45] [m]	5 [45] [i, n]	0 [i]	5 [45] [n]
van Tol, 2000 [o]	11	11	1 [9]	2 [18] [p]	1 [9]	0 [p]	1 [9] [q]	10 [92] [r]
Muros, 2000	10	9	ND	4 [44]	0	ND	ND	5 [56] [s]
Stokkel, 1999	10	7	7 [100]	ND	ND	ND	ND	ND
Total [t]	97	79	21 [36]	37 [51]	21 [29]	21 [33]	12 [34]	23 [32]
Total w/o van Tol, 2000 [u]	86	68	20 [43]	35 [56]	20 [32]	21 [40]	11 [46]	13 [21]

N, Number of subjects in study with differentiated thyroid cancer, elevated Tg, and negative WBS; n, number of subjects; %, percent of subjects with positive PET who had noted management decision; Cure, Reported cure, using each study's definition; No Change, No change in management reported (does not include other non-surgical diagnostic procedures); ND, No data

[a] 29 subjects reported to have change in management due to PET. Possibly subject who declined further treatment had negative PET scan. Percentages based on 29 subjects.

[b] 3 had biopsy after positive PET and CT or US; unclear if PET affected decision to perform biopsy.

[c] Disease was pathologically confirmed in 20.

[d] 4 had external radiotherapy; 1 had differentiation therapy to stimulate ^{131}I uptake.

[e] Mean follow-up 6 months (range, 3-24 months).

[f] Included in Table 1 under Wang, 2000.

[g] Including 1 false positive PET, resulting in biopsy and therapeutic WBS (patient had no evident disease, but continued to have elevated Tg). 3 subjects had both surgery and radioiodine ablation.
[h] 2 subjects had retinoic acid treatment
[i] No data on duration of follow-up.
[j] 1 with no evidence of disease. 1 classified as false positive, with no evidence of disease except elevated Tg.
[k] 3 had limited disease and 8 had diffuse disease.
[L] 1 with diffuse disease; 1 with limited disease.
[m] 6 patients (55%) total had change in management; 3 had both surgery and radioiodine ablation.
[n] No data on follow-up disposition of 1 subject. 1 subject refused further surgery despite advancing disease; 4 false positive scans.
[o] Letter to the Editor
[p] 2 subjects had cervical lymphadenectomy with no metastatic tumor found.
[q] At 3 years.
[r] Not including biopsies. No clinically apparent disease in all 10 after median follow-up of 32 months (range, 17-33 months).
[s] Implied. No data on disposition.
[t] Lind, 2000 not included. Percentages refer to percent of positive PET scans in studies with data. Due to incomplete reporting, percentages may not add up to 100%.
[u] Data analyzed excluding the Letter to the Editor by van Tol (2000) which explicitly ignored most PET results in determining patient management.

Table 5. Test performance of PET for Medullary thyroid cancer

Study	TP (n)	FN (n)	TN (n)	FP (n)	Sensitivity (%)	Specificity (%)	Prevalence of Metastatic Thyroid Cancer (%)
Elevated calcitonin and Negative imaging tests							
Adams, 1998 EJNM [a]	5	0	1	0	100	[100]	83
Musholt, 1997 [a]	2 [b]	0 [b]	1	1 [b]	100 [b]	50 [b]	50
Adams, 1998 NMC [a]	2	0	0	0	100	--	100
Conti, 1999 [a]	1	0	0	(1 [c])	[100]	[0]	-- [c]
Gasparoni, 1997	1 [d]	1 [d]	0	0	50 [d]	--	100
Simon, 1996	1	0	0	0	[100]	--	100
Elevated calcitonin							
Brandt-Mainz, 2000	13 [e]	4	0	0 [e]	76 [e]	-- [e]	100 [e]
Adams, 1998 EJNM	7	0	1	0	100	[100]	88
Musholt, 1997	6 [b]	0 [b]	1	1 [b]	100 [b]	50 [b]	75
Adams, 1998 NMC	5	0	0	0	100	--	100
Conti, 1999	2-4 [f]	0	0	(3-1 [c, f])	100 [f]	[0] [f]	-- [f]

TP = true positive; FN = false negative; TN = true negative; FP = false positive; n = number of subjects.
Studies in bold have at least 10 subjects in each group with and without metastatic disease
Sensitivity or specificity results in brackets are based on only one subject.

[a] Subset of full study shown in bottom half of Table 5.

[b] One subject had 1 lesion on PET that was a false positive; however a true metastasis found by surgery was missed on PET (false negative). In this table, this subject is treated as a true positive, since positive PET may have resulted in surgical exploration that yielded positive diagnosis.

[c] One subject had no further treatment over 2 year follow-up. Study had no true reference standard.

[d] According to Table, 1 subject (with sporadic disease) had false negative PET after treatment. According to text, the subject with the false negative PET had MEN IIa. This subject had PET as part of preoperative staging (according to the Table). If text is correct, then both subjects with PET after treatment had true positive tests (sensitivity = 100%)

[e] Two subjects with positive PET were excluded because diagnostic confirmation was not performed.

[f] One patient treated with interferon, calcitonin continued to rise. One subject had no treatment, had had positive surgical margins, and calcitonin continued to rise. Study had no true reference standard. One subject with positive PET was lost to follow-up.

Table 6. Change in clinical management of medullary thyroid cancer directed by PET
Elevated Calcitonin and Negative other imaging

Study, Year	**N**	**Positive PET** (n)	**Surgery** (n [%])	**Non-surgical treatment** (n [%])	**Cure** (n [%])	**Recurrence** (n [%])	**No Change** (n [%])
Elevated calcitonin and Negative imaging tests							
Lind, 2000	8	ND	2	ND	2 [a]	0	6 [b]
Simon, 1996	1	1	1 [100]	0	1 [100] [c]	0 [c]	0
Elevated calcitonin							
Brandt-Mainz, 2000	19 [d]	15	9 [60]	ND	ND	ND	6 [40] [e]
Adams, 1998 EJNM	8	7	2 [28]	ND	ND	ND	6 [86] [e]
Musholt, 1997	8	7	8 [100] [f]	ND	ND	ND	8 [100] [f]
Conti, 1999	6	6	2 [33]	1 [17] [g]	ND	ND	2 [33] [h]
Adams, 1998 NMC	5	5	5 [100]	ND	3 [60] [e]	2 [40] [i]	0

N, Number of subjects in study with medullary thyroid cancer, elevated calcitonin and/or CEA, and negative "standard imaging" (see Table 2, Part III, Comments); n, number of subjects;
Cure, Reported cure, using each study's definition; No Change, No change in management reported (does not include other non-surgical diagnostic procedures); ND, No data

[a] No data on follow-up duration
[b] 6 subjects had distant metastases
[c] "To date"
[d] Including two subject excluded from analysis because diagnostic confirmation not done.
[e] Implied
[f] All subjects, including one with negative PET had cervical lymph node dissection or debulking.
[g] Interferon treatment
[h] One subject lost to follow-up
[i] At one year

Table 7. Potentially False Positive PET [a]

Study	Pt #	Sex	Age	Histology	Location	Tg [b]	WBS	CT	MRI	US	Biopsy	Duration	Method of Dx
Alnafisi, 2000	FP 1	M	38	Papillary	Thyroid	8/25	–	–	ND	–	ND	ND	CT, US, Obs
	FP 2	F	19	Papillary	Thyroid	<1/47	–	Lung [c]	ND	–	ND	ND	US, Obs
	FP 3	F	38	Papillary	Thyroid, R neck	5/437	–	+	ND	+	Non-Dx	ND	FNA, Obs
	FP 4	F	40	Papillary	R neck	<1/51	–	+	ND	+	Normal	ND	FNA, Obs
Chung, 1999	FP 1	ND	ND	Papillary	Mediastinum	ND	–	ND	ND	ND	TB		Biopsy
Grunwald, 1997[d]	FP 1	ND	ND	Diff't'ed	Sites: 1 Thyroid 3 LN 1 Distant	18	–	ND	ND	ND	–		Histology [e]
	FP 2	ND	ND	Diff't'ed		1	–	ND	ND	ND	–		Histology [e]
	FP 3	ND	ND	Diff't'ed		< 1	–	ND	ND	ND	–		Histology [e]
	FP 4	ND	ND	Diff't'ed		< 1	–	ND	ND	ND	–		Histology [e]
Grunwald, 1999[d]	FP 1	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	Overall clinical evaluation including histology, cytology, Tg level, US, CT, clinical course
	FP 2	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 3	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 4	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 5	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 6	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 7	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 8	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 9	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 10	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
	FP 11	ND	ND	Papillary	ND	< 5	–	ND	ND	ND	ND	ND	
Helal, 2001	FP 1	F	37	Papillary	Cervical LN	10/121	– other imaging				Inflam LN		Surgery
	FP 2	F	45	Papillary	Cervical LN	3/30	– other imaging				Inflam LN		Surgery
	FP 3	F	55	Papillary	Cervical LN	55/178	– other imaging				Inflam LN		Surgery
Muros, 2000	FP 1	ND	ND	Follicular	Cervical spine	500	–	ND	–	ND	ND	ND	MRI
	FP 2	ND	ND	Follicular	Mediastinum (Thymus)	21	–	ND	ND	ND	ND	ND	ND
	FP 3	ND	ND	Papillary	Anterior mediastinum	150	–	–	ND	ND	ND	ND	CT, CXR
van Tol, 2000 [f]	FP 1	F	52	Papillary	Cervical LN	7	–	– CT or MRI		ND	–	23 months	Biopsy
	FP 2	F	52	Papillary	Cervical LN, Pharynx	4	–	– CT or MRI		ND	–	31 months	Biopsy
Wang, 1999	FP 1	F	54	Papillary	Lungs	< 1	ND	+	ND	ND	Granuloma		Biopsy
	FP 2	F	78	Follicular	Lung	< 1	ND	–	ND	ND	ND	1 year	CT follow-up
	FP 3	M	77	Papillary	Humerus	88	ND	? Lung	ND	ND	Fibrous dysplasia		Biopsy
	FP 4	F	59	Papillary	Tracheostomy	5	–	ND	ND	ND	Inflammation	ND	ND

Musholt, 1997	FP 1 / FN 1 [g]	M	52	Sporadic Medullary	FP: Cervical FN: Cervical	1.7 [h]	– other imaging	ND	FP: – FN: +		Systemic LN dissection

CT, computed tomography; CXR, chest x-ray (plain radiography); Diff't'ed, differentiated thyroid cancer; Dx, diagnosis; F, female; FN, false negative; FNA, fine needle aspiration biopsy; FP, false positive; Inflam, inflamed; LN, lymph nodes; M, male; MRI, magnetic resonance imaging; ND, no data; non-Dx, non-diagnostic; Obs, observation; Pt, patient; R, right; TB, tuberculosis; Tg, thyroglobulin; US, ultrasonography; WBS, ^{131}I whole body scintigraphy; –, negative test result; +, positive test result; ?, possible mass

[a] Not all cases reported as false positives in the studies had histological evidence that lesions were truly not malignancies, as noted.
[b] Thyroglobulin in ng/mL. When two numbers reported, first is suppressed Tg level, second is non-suppressed Tg level.
[c] CT discordant with PET.
[d] Subjects reported in Grunwald, 1997 probably also included in Grunwald, 1999.
[e] Implied.
[f] Letter to the Editor
[g] One subject had both a false positive lesion and a false negative lesion. Lesion seen by PET was not cancer, but a metastasis found by cervical lymph node dissection was missed by PET.
[h] Calcitonin level in ng/mL.

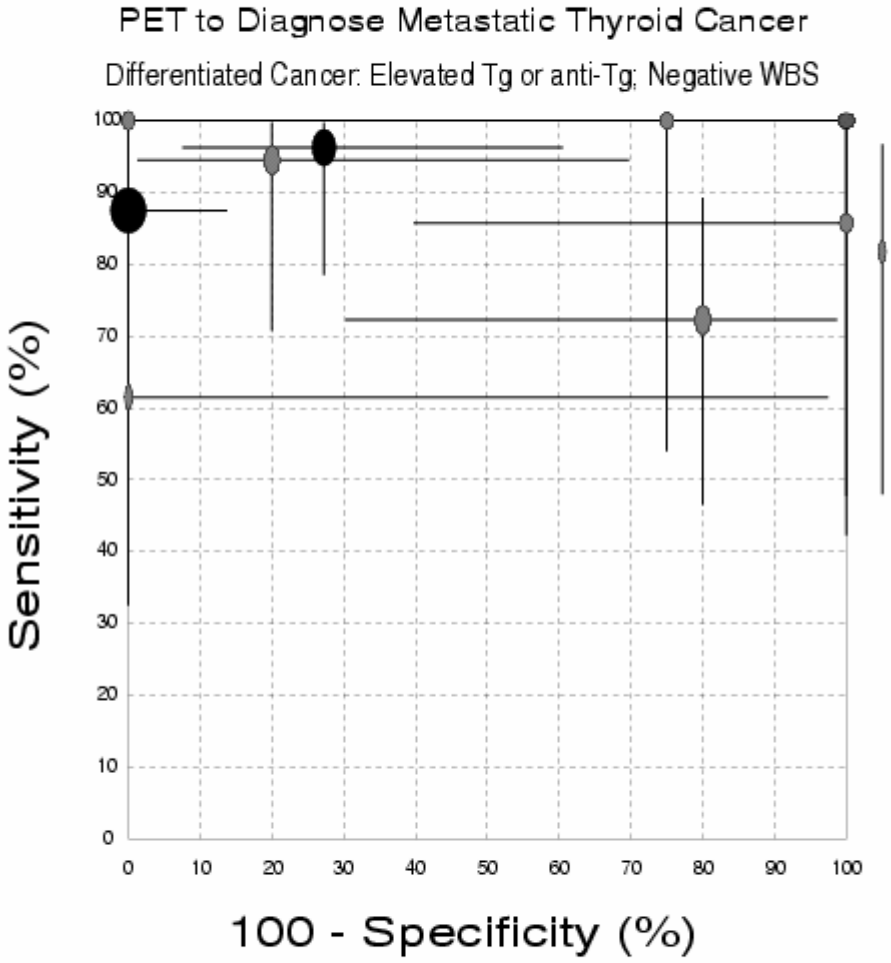
PET to Diagnose Metastatic Thyroid Cancer
Differentiated Cancer: Elevated Tg or anti-Tg; Negative WBS
Sensitivity (%)
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
60
70
80
90
100
100 - Specificity (%)

Figure 1. Test performance of PET to diagnose metastatic disease (N=10). The ellipses represent the sensitivity and specificity (100%-specificity) of the individual studies of PET to diagnose metastases in patients with treated differentiated thyroid cancer. Patients in these studies have elevated thyroglobulin (Tg) and negative ^{131}I whole body scintigraphy. Each study shown in this figure has at least 10 patients. The x- and y-dimensions of the ellipses are proportional to the square root of the number of patients available to study the specificity and sensitivity, respectively. The vertical and horizontal lines represent the 95% confidence interval for the sensitivity and specificity, respectively, of each study.

The black ellipses represent “large” studies with at least 10 subjects in both with and without metastatic disease groups. The gray ellipses represent the smaller studies. The ellipse outside the graph represents the study that had no subjects without metastatic disease; therefore specificity could not be determined. (13).

Two studies with different possible interpretations of eligible subjects are plotted using the more inclusive criteria for each. For Chung (1999), the subject with a false positive scan is included. (8) For Wang (1999), subjects with either elevated Tg or anti-Tg antibody are included. (9) Grunwald (1997) is not included because of incomplete data. (12) See Table 3.

ABBREVIATIONS

af, all fields (Medline)
CEA, carcinoembryonic antigen
cm, centimeter
CMS, Centers for Medicare and Medicaid Services
CT, computed tomography
CXR, chest X-ray (plain radiography)
Diff't'ed, differentiated thyroid cancer
DMSA, ^{99m}Tc(V)-dimercaptosuccinic acid scintigraphy
Dx, diagnosis
EJNM, European Journal of Nuclear Medicine
exp, explode (Medline)
F, female
FDG, 2-[18F] fluoro-2-deoxy-D-glucose
FN, false negative
FNA, fine needle aspiration biopsy
FP, false positive
HCFA, Health Care Financing Administration
hr, hour
Inflam, inflamed
IV, intravenous
L, liter
LN, lymph node
M, male
MBq, milliBecqueral
mCI, milliCurie
MDP, ^{99m}Tc methylene diphosphonate scintigraphy
MIBI, ^{99m}Tc sestamibi scintigraphy
min, minutes
mL, milliliter
MRI, magnetic resonance imaging
MTC, medullary thyroid cancer
N/n, number
ND, no data
ng, nanogram
NMC, Nuclear Medicine Communications
Non-Dx, non-diagnostic
PET, positron emission tomography
Pt, patient

rn, registry number (Medline)
ROC, receiver operating charachteristics
SRS, somatostatin receptor scintigraphy
SUV, standardized uptake value
TB, tuberculosis
Tg, thyroglobulin
TN, true negative
TP, true positive
TSH, thyroid stimulating hormone
US, ultrasonography
WBS, ^{131}I whole body scintigraphy
y, years old
yr, year (Medline)
$, wild card (Medline)