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# Real-Time Prognosis for Metastatic Thyroid Carcinoma Based on 2-[$^{18}$F]Fluoro-2-Deoxy-D-Glucose-Positron Emission Tomography Scanning

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**Context/Objective:** Approximately 15% of thyroid cancer patients develop subsequent metastases. The clinical course of patients with metastatic thyroid carcinoma is highly variable. We hypothesized that the metabolic activity of metastatic lesions, as defined by retention of 2-[$^{18}$F]fluoro-2-deoxyglucose (FDG), would correlate with prognosis.

**Design/Patients:** The initial FDG-positron emission tomography (PET) scans from 400 thyroid cancer patients were retrospectively reviewed and compared with overall survival (median follow-up, 7.9 yr). We examined the prognostic value of clinical information such as gender, age, serum thyroglobulin, American Joint Committee on Cancer (AJCC) stage, histology, radioiodine avidity, FDG-PET positivity, number of FDG-avid lesions, and the glycolytic rate of the most active lesion.

**Results:** Age, initial stage, histology, thyroglobulin, radioiodine uptake, and PET outcomes all correlated with survival by univariate analysis. However, only age and PET results continued to be strong predictors of survival under multivariate analysis. The initial American Joint Committee on Cancer stage was not a significant predictor of survival by multivariate analysis. There were significant inverse relationships between survival and both the glycolytic rate of the most active lesion and the number of FDG-avid lesions.

**Conclusions:** FDG-PET scanning is a simple, expensive, but powerful means to restage thyroid cancer patients who develop subsequent metastases, assigning them to groups that are either at low (FDG negative) or high (FDG positive) risk of cancer-associated mortality. We propose that the aggressiveness of therapy for metastases should match the FDG-PET status. **(*J Clin Endocrinol Metab* 91: 498–505, 2006)**

THYROID CANCER PROGNOSIS paradigms in current use, *e.g.* tumor node metastasis (TNM); age, metastases, extrathyroid extension, tumor size (AMES); and metastasis/age/completeness of resection/invasion/size (MACIS), have proven to be useful for predicting overall survival. These systems are based on clinical and pathological data obtained at time of initial diagnosis (1–5). The presence of distant metastases (DM) at initial diagnosis is a negative prognostic factor in virtually all of these models. There are usually no provisions, however, to restage or update the prognosis when subsequent metastases develop. It is not clear, for instance, that the survival of a 60-yr-old stage I patient who develops lung metastases 20 yr after the initial diagnosis is different from that of a 60-yr-old who is found to have lung metastases at initial diagnosis. Both are 60 yr old with DM, but the TNM or metastasis/age/completeness of resection/invasion/size scoring systems would suggest a worse prognosis for the patient with the DM found at initial diagnosis. This may be correct, but there are few primary data to support this prediction. Prognostication in the setting of a newly diagnosed DM would benefit by an assessment that would stay current with the real-time clinical status. Because thyroid carcinoma is now the cancer with the highest annual percentage increase in incidence of any cancer in the United States (6), it is likely that more patients with thyroid cancer metastases will need evaluation and management.

Survival from the time of discovery of DM has not been well studied, but appears to have a wide variation. In a series from the Mayo Clinic, 24% of patients with recurrent thyroid cancer survived for at least 15 yr after the DM was discovered (7). A multivariate analysis of this cohort revealed that older age and metastases in multiple tissues were associated with significantly shorter survival. A retrospective review from Memorial Sloan-Kettering found that 26% of patients were alive 10 or more yr after recurrent DM was discovered (8). A multivariate analysis of this cohort revealed that age over 45 yr, symptoms from the metastases, metastases in multiple sites, and no radioiodine treatment were all significantly associated with a shorter survival. For patients over 45 yr of age, there was no apparent difference in survival between those whose DM was discovered within 6 months of initial diagnosis, compared with DM found more than 6 months after initial diagnosis. It is clear that patients with DM have a worse prognosis. The problem has been the inability to

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Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; DM, distant metastases; FDG, 2-[$^{18}$F]fluoro-2-deoxy-D-glucose; PET, positron emission tomography; RR, relative risk; $SUV_{max}$, standard uptake value of the most active lesion; Tg, thyroglobulin; TNM, tumor node metastasis.

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quantify the average survival time, which has important implications for treatment decisions.

The present study is based on our preliminary observations that 2-[$^{18}$F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET) scans produced data (*i.e.* tumor volume and estimates of lesional glycolytic rate) that had prognostic implications for patients with metastatic thyroid carcinoma (9). We have expanded our cohort and have extended our follow-up interval to define, with greater statistical power, the relationship between the FDG scan results and survival for patients with thyroid cancer metastases. We propose that an FDG scan can serve as a real-time assessment of prognosis with defined survival rates at specified intervals, thereby enabling patients and their physicians to make more informed decisions about the timing and aggressiveness of therapeutic interventions.

## Patients and Methods

This study was reviewed and approved by the Memorial Sloan-Kettering Cancer Center Institutional Review Board/Privacy Board. The board granted a waiver of authorization (WA0067-05) for informed consent based on maintaining confidentiality of each patient's identity and all personal health information. We reviewed the records of all FDG-PET scans performed on thyroid cancer survivors at our medical center between January 1996 and June 2003 (n = 907). Many of the patients had more than one scan. Patients were referred for FDG scanning by many different attending physicians for a variety of reasons. Initially, many of these patients were selected to evaluate the usefulness of the new technique for the surveillance of thyroid cancer survivors. As more experience was gained with FDG-PET, the test was used more selectively. The most common reasons for current referrals are the presence of an elevated serum thyroglobulin (Tg) level in the setting of a negative radioiodine whole-body scan or for surveillance in Hürthle cell carcinoma (10). Thus, this group of thyroid cancer survivors is somewhat heterogeneous. For this analysis, we chose to include only the first scan from any patient who had multiple scans so as not to weight the results toward individuals with more aggressive disease. Furthermore, we included only patients whose FDG scans were retrievable for independent review. Patients with medullary thyroid carcinoma, thyroid lymphomas, or any other active cancers (n = 52) were eliminated from the analysis. Patients with systemic inflammatory diseases (*e.g.* sarcoidosis, systemic lupus erythematosus) were also excluded (n = 17). The initial FDG scans of 400 patients with follicular cell-derived thyroid carcinoma met the criteria for inclusion in the final analysis. All patients suspected of having residual thyroid cancer underwent conventional assessments including neck ultrasonography, computerized tomography, magnetic resonance imaging, chest x-rays, and/or bone scans as routine standard care.

### *FDG-PET scans*

Images were acquired on a General Electric Advance PET camera, the Discovery LS PET/computed tomography (CT) scanner (General Electric Medical Systems, Milwaukee, WI) or the Biograph PET/CT scanner (CTI, Siemens Medical Systems, Malvern, PA) as previously described (9). Patients were fasted for at least 6 h before iv injection of 444 MBq of FDG for adults (normalized by body surface for children). About 1 h after injection, FDG emission images were recorded from the base of skull to the midthighs. After iterative reconstruction, images were corrected for attenuation and displayed in the coronal, sagittal, and transverse section for interpretation. When patients were imaged with PET/CT, the associated CT images were evaluated in the same planes for anatomic reference. When available, fused PET/CT images were also reviewed. The scans were inspected visually and sites of abnormally increased uptake were counted and grouped by location. In addition, the standard uptake value of the most active lesion ($SUV_{max}$) was identified. The FDG-PET images were read, on two separate occasions, once by a team of two experienced nuclear medicine physicians and later by an independent senior nuclear medicine physician. Any significant differences in interpretations were adjudicated during a meeting of all three physicians. The image reviewers were blinded to clinical and laboratory information. Lesions were counted as any separated uptake focus, regardless of size. Individuals with 10 or more separate lesions were counted as 10 lesions for statistical analysis. The site of an individual metastatic lesion was grouped as neck (above sternal notch and below ears), mediastinum, lungs, bone, and other (*e.g.* brain, liver, adrenal). Whenever the tissue that harbored a lesion was uncertain and could not be assigned to one of the aforementioned groups, they were assigned as others.

Sixty-three percent of the positive FDG scans were performed in patients whose TSH was suppressed by $T_4$, whereas the rest were performed on patients with TSH levels above 5 $\mu$U/ml. The $SUV_{max}$ was not statistically different between the group with a suppressed TSH (median $SUV_{max}$ 10.4; range, 1.9–53; n = 98; for those with a TSH $< 0.4$ $\mu$U/ml) and the group with an elevated TSH (median $SUV_{max}$ 11.8; range, 2.1–41; n = 72; for those with a TSH $> 5.0$ $\mu$U/ml). The median TSH for those with an elevated TSH was 70.6 mU/liter (range, 5.2–568 mU/liter). We therefore combined all the $SUV_{max}$ readings, regardless of the TSH level.

### *Whole-body 131-I scans*

Whole-body radioiodine scans were conducted and interpreted as previously reported (11). To be considered for this analysis, a radioiodine whole-body scan had to be performed within 6 months of the FDG scan. Seventy-eight patients did not have a comparable radioiodine scan within this time frame. The most informative scan (either a diagnostic or posttherapy scan) during that interval was used to determine radioiodine avidity status. All radioiodine scans were read by Memorial Sloan-Kettering Cancer Center attending nuclear medicine physicians before their knowledge of this analysis, and the results were taken from their official reports.

### *Clinical chemistry and pathology*

Serum TSH and Tg were measured as previously reported (12). Surgical specimens of primary tumors were obtained on all patients and were reviewed by attending board-certified pathologists at Memorial Sloan-Kettering Cancer Center.

### *Clinical staging*

The TNM stage of the patient was determined according to the American Joint Committee on Cancer (AJCC)-International Union Against Cancer format (fifth edition) (4). The sixth edition of the thyroid cancer TNM staging system (13) became active in January 2003. It has many new substages and has redefined the size of T1 tumors. The sixth edition has generated controversy (14). Because no prospective trials have yet validated the new system, we have chosen to use the well-established fifth edition for this study.

### *Determination of overall survival*

The medical records of all patients were updated during a 30-d period ending on July 1, 2003. We recorded the date of death for all deceased subjects and the most recent office visit for all surviving patients.

### *Statistical methods*

Overall survival, as measured by the time between the date of PET scan and date of death or last follow-up, is the primary end point of this study. Survival probabilities were estimated by the Kaplan-Meier method and compared using the log-rank test. $SUV_{max}$ and the number of lesions were categorized using observed quartiles to avoid bias and to improve presentation.

## Results

### *Patient and tumor characteristics*

The initial FDG scans of 400 thyroid cancer survivors were analyzed. Approximately 55% (221 of 400) of the scans were

interpreted to be abnormal. As shown in Table 1, the patients who had abnormal scans were older, less likely to be female, more likely to have a concomitant-positive radioiodine whole-body scan, and less likely to be stage I/II than were those who had normal FDG scans. The median serum Tg level was 44 ng/ml (range, 0.3–214,000 ng/ml) in the FDG-positive group and 1 ng/ml (range, 0.3–128 ng/ml) in the FDG-negative group. Metastases were identified in 33.9% of the FDG-negative patients (by ultrasound, CT, radioiodine, and magnetic resonance imaging scans) and all of the FDG-positive patients. Histopathologic subtypes for the entire cohort are shown in Table 2. The highest 2-yr survivals occurred in those with classical papillary thyroid carcinoma and those with Hürthle cell carcinoma (Table 2). Papillary thyroid carcinoma and it variants were more common in the FDG-negative group (Table 1). Survival was significantly lower ($P < 0.001$) for those with anaplastic and poorly differentiated thyroid carcinoma. The 2-yr survival for anaplastic thyroid carcinoma was only 32% (Table 2).

Median follow-up for the entire group from the time of diagnosis was 7.9 yr (range, 0.15–39.7 yr). Median follow-up from the time of the PET scan was 3.04 yr (range, 0–6.9 yr). The median follow-up for survivors only was 6.2 yr (range, 0.17–36.5 yr). At the end of the study (Table 3), in the FDG-positive group, there were 100 patients alive with disease, 32 alive with no evidence of disease, and 89 patients had died. In the FDG-negative group, there were 73 patients alive with disease, 102 alive with no evidence of disease, and four patients had died. Two deaths in the FDG-negative group and two in the FDG-positive group were clearly unrelated to thyroid cancer, but they are included in the overall survival analysis.

*Univariate analyses of factors predicting survival*

We investigated the influence of a number of clinical features on survival using univariate analysis. These included: gender, age at PET, radioiodine avidity, original histology, AJCC stage, FDG scan result, the $SUV_{max}$, and the number of FDG-avid lesions. As shown in Table 2, gender did not influence overall survival (Fig. 1A), whereas age at the time of the PET scan had a dramatic effect on survival (Fig. 1B). The TNM stage (Fig. 1C) also correlated with survival.

The uptake of radioactive iodine correlated with overall survival (Fig. 2A). Individuals with scans that concentrated radioiodine had a significantly reduced survival, compared with those that did not ($P = 0.03$). This was due, in part, to the fact that many patients who had negative radioiodine scans were often judged to have no evidence of disease. When only patients with metastatic disease were compared, there was no difference in overall survival between those whose lesions retained radioiodine and those that did not (see Fig. 5A). However, a positive FDG scan had a very strong ($P < 0.001$) negative influence on survival (Fig. 2B). When both the radioiodine and FDG scans are considered together in each patient, four categories are created; as shown in Fig. 2C, the FDG positivity had a much larger influence on survival than did the radioiodine avidity ($P < 0.001$).

The estimated glycolytic rate of the most active FDG-avid lesion (the $SUV_{max}$) correlated negatively with survival ($P < 0.001$). The $SUV_{max}$ readings are depicted in Fig. 3A as either no uptake or four quartiles (n = 56 patients each) of magnitude. Two-year survival probabilities were 99% in the negative group, 98% in the lowest quartile, 73% in the second quartile, 70% in the third, and 52% in the quartile with the highest $SUV_{max}$. The number of FDG-positive lesions in each individual was also determined. We divided the entire co-

**TABLE 1.** Patient characteristics

| | All | FDG-Neg | FDG-Pos |
|---|---|---|---|
| N | 400 | 179 | 221 |
| Age (mean ± SD) | 53.8 ± 16.1 | 47.3 ± 14.4 | 59.1 ± 15.5 |
| Female (%) | 56.3 | 63.7 | 50.2 |
| FDG (mCi) | 11.4 ± 2.2 | 11.3 ± 2.1 | 11.4 ± 2.2 |
| Median TSH ($\mu$U/ml) | 0.32 | 0.27 | 0.52 |
| Median Tg (ng/ml) | 4.9 | 1.0 | 44.0 |
| RAI scan positive (%) | 62.0 | 50.1 | 71.4 |
| Papillary (%) | 69.2 | 75.4 | 64.2 |
| Stage I–II (%) | 48.7 | 69.8 | 31.6 |
| Expired | 93 | 4 | 89 |

RAI, $^{131}$I-iodine scan; stage, AJCC stage, 5th ed; papillary, includes classical papillary and variants; Neg, negative; Pos, positive.

**TABLE 2.** Univariate analyses

| Risk factor | Patients (n) | Deaths (n) | *P* value | Survival, % (2 yr) |
|---|---|---|---|---|
| Age at FDG-PET (yr) | | | <0.01 | |
| <45 | 119 | 7 | | 96 |
| ≥45 | 281 | 86 | | 81 |
| Gender | | | 0.28 | |
| Female | 225 | 49 | | 87 |
| Male | 175 | 44 | | 84 |
| Serum Tg | | | <0.01 | |
| ≤2 ng/ml | 140 | 9 | | 93 |
| >2 ng/ml | 212 | 71 | | 82 |
| AJCC stage | | | <0.01 | |
| I | 139 | 11 | | 95 |
| II | 56 | 7 | | 90 |
| III | 133 | 41 | | 83 |
| IV | 62 | 31 | | 70 |
| Pathology | | | <0.01 | |
| Papillary | 201 | 30 | | 92 |
| Papillary variants | 76 | 13 | | 89 |
| Follicular | 31 | 12 | | 79 |
| Hürthle | 36 | 7 | | 91 |
| Poorly differentiated | 45 | 24 | | 70 |
| Anaplastic | 11 | 7 | | 32 |
| RAI uptake | | | 0.03 | |
| Positive | 177 | 53 | | 81 |
| Negative | 122 | 20 | | 91 |
| Thyroid bed only | 23 | 3 | | 96 |
| Not available[a] | 78 | 7 | | 82 |

AJCC stage based on 5th ed; RAI, 131-iodine whole-body scan result. There were three deaths in the 10 patients who could not be staged.

[a] RAI scans had to be performed within 6 months of the date of the FDG scan.

**TABLE 3.** Final survival status

| | AND | AWD | DOD | DWD | DND |
|---|---|---|---|---|---|
| All patients (n = 400) | 134 | 173 | 89 | 2 | 2 |
| FDG-PET positive (n = 221) | 32 | 100 | 87 | 1 | 1 |
| FDG-PET negative (n = 179) | 102 | 73 | 2 | 1 | 1 |

AND, Alive no evidence of disease; AWD, alive with disease; DOD, died of disease; DWD, died with disease; DND, died no evidence of disease.

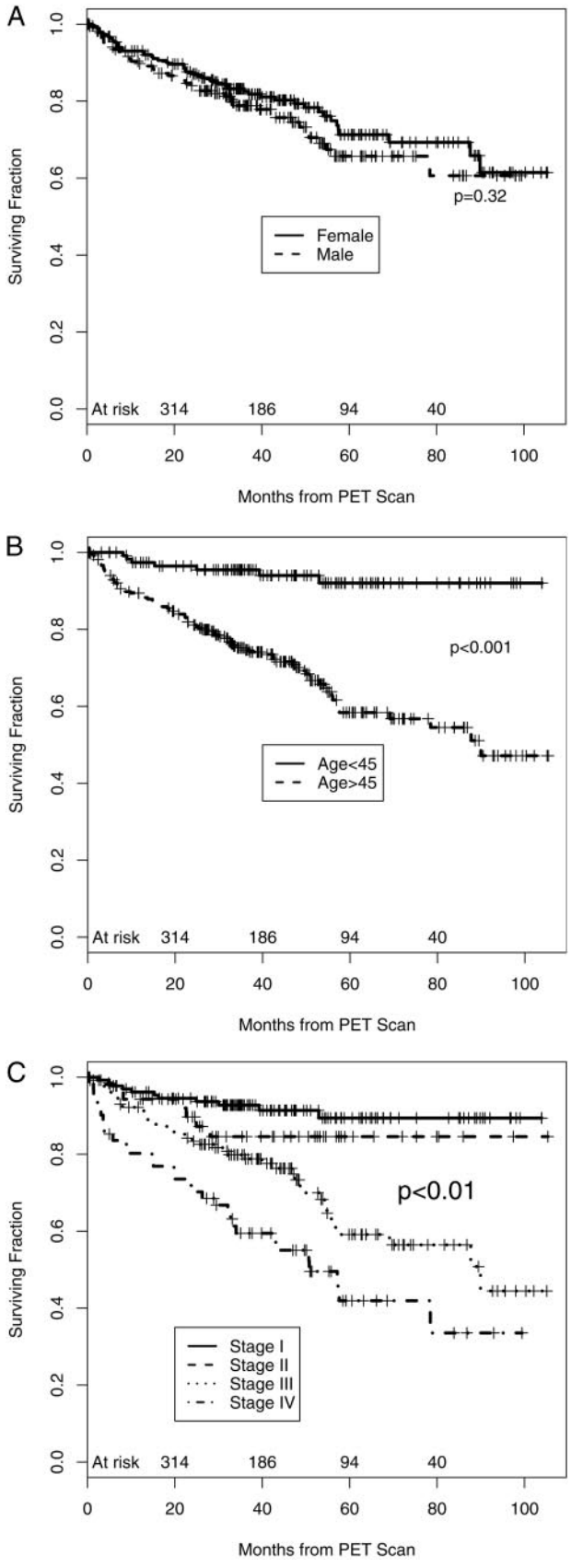


FIG. 1. Kaplan-Meier survival plots of thyroid cancer patients based on gender (A), age (B), and AJCC stage (C).

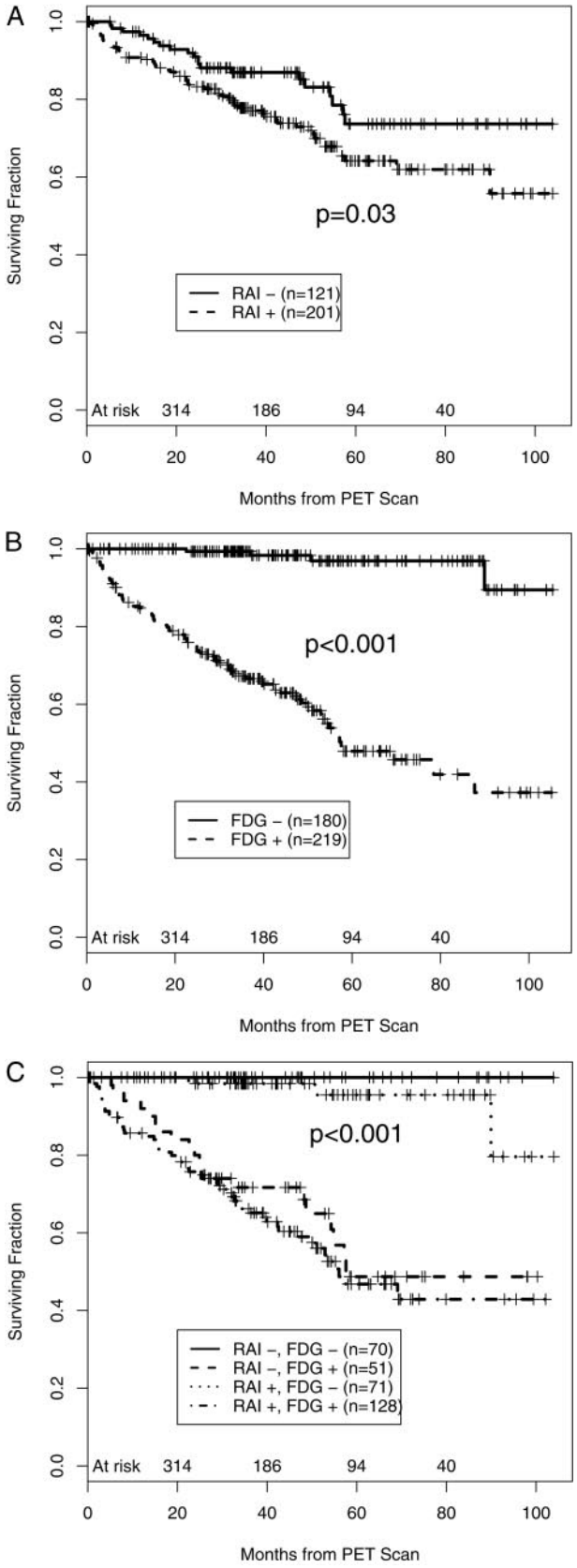


FIG. 2. Kaplan-Meier survival plots of thyroid cancer patients based on radioactive iodine scanning (A), FDG-PET scanning (B), and combination scanning (C). −, Scan negative; +, scan positive.

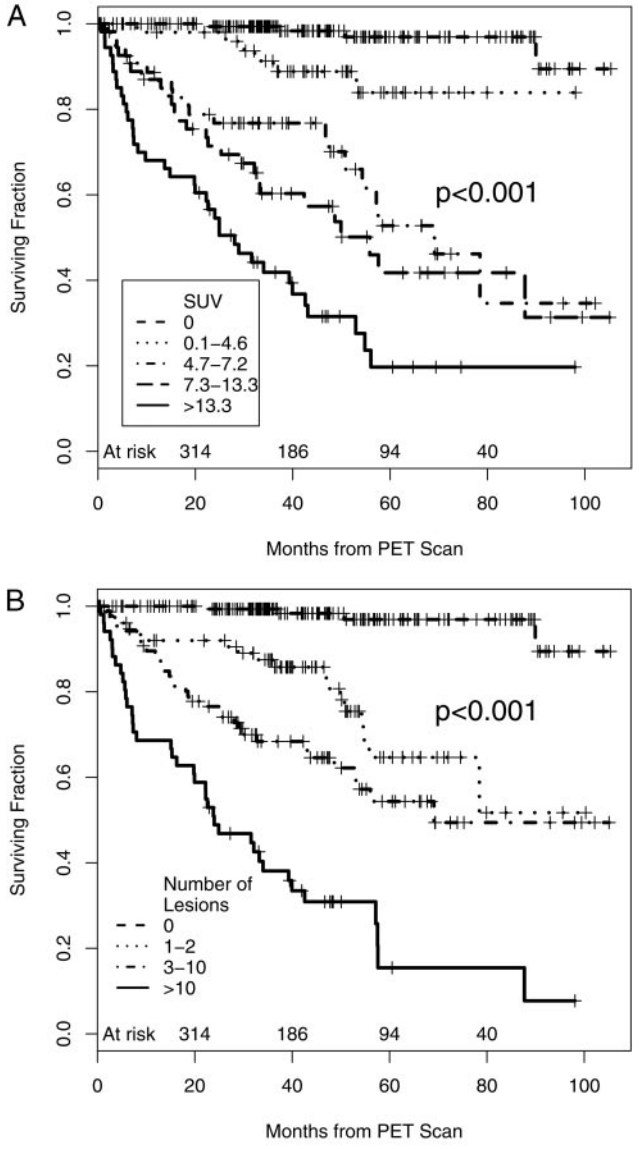


FIG. 3. Kaplan-Meier survival plots of thyroid cancer patients based on PET scan $SUV_{max}$. Positive scans were divided into quartiles (A) or on the number of FDG-positive lesions (B). SUV, Standard uptake value of the most active lesion.

hort into four categories [no lesions (n = 181), one to two lesions (n = 83), three to 10 lesions (n = 92), and more than 10 lesions (n = 51)] for a log-rank analysis. There was a highly significant overall reduction in survival ($P < 0.001$) as the number of lesions increased (Fig. 3B).

The survival of those with FDG-positive scans was also analyzed based on the site of the metastasis. Those with local FDG-avid lesions restricted to the neck had the best survival, those with regional metastases (in the supraclavicular or mediastinal regions) fared slightly worse, and those with distant metastases had the lowest overall survival (Fig. 4). When we considered only those who had metastatic disease, the influence of radioiodine-avidity status on survival dropped out (Fig. 5A). Patients in Fig. 5A who had no metastases, but did have radioiodine uptake, all had minimal uptake in the thyroid bed only. On the other hand, the FDG

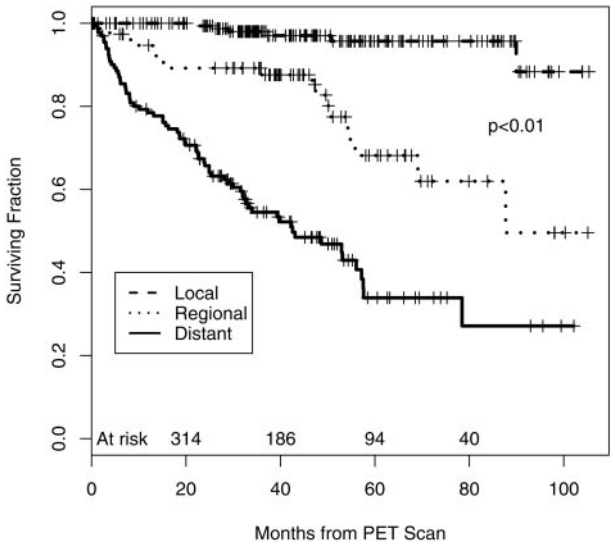


FIG. 4. Kaplan-Meier survival plots of thyroid cancer patients based on the location of metastases. Local, Local metastases in thyroid bed or in cervical lymph nodes; regional, metastases in supraclavicular or mediastinal areas; distant, distant metastases.

avidity of metastases had a major influence on survival (Fig. 5B). Of those with negative FDG scans, there was no statistical difference in survival between those with or without metastases ($P = 0.29$). When the status of the FDG scan is integrated with the TNM stage (Fig. 6), it appears that survival of stages I-III patients who have positive FDG scans is very similar to that of stage IV patients. On the other hand, the survival of stage I-III patients who had negative FDG scans was excellent and was statistically different from stage I-III patients who had positive FDG scans ($P < 0.001$).

The serum Tg level (on $T_4$ suppression) also independently correlated with survival. Of the 140 patients with a serum Tg 2 ng/ml or less at the time of the FDG scan, there were nine deaths. Of the 212 patients with a Tg greater than 2 ng/ml, there were 71 deaths ($P < 0.01$). The Tg levels at the time of the PET scans were unmeasurable in 13 patients due to interfering substances in their blood and were not drawn in 35 patients.

### *Multivariate analysis*

The following variables were included in the multivariate analysis: age at PET (used as a continuous variable), AJCC stage, histopathology, gender, serum Tg on $T_4$ suppression, radioiodine avidity, FDG avidity, the number of FDG avid lesions per patient, and the site of the metastases. Using a Cox proportional hazard model, we found that age [relative risk (RR) 1.33; 95% confidence interval 1.08–1.52], FDG status (RR 7.69; 95% confidence interval 2.17–24.4), and the number of FDG lesions (RR 1.1; 95% confidence interval 1.08–1.15) significantly correlated with survival. Because the $SUV_{max}$ and FDG status overlap considerably, they were not considered together for the multivariate analysis. When $SUV_{max}$ (as a continuous variable) was substituted for the number of FDG-positive lesions in the multivariate analysis, the $SUV_{max}$ was also a significant (RR 1.1; 95% confidence interval 1.04–1.17) predictor of survival.

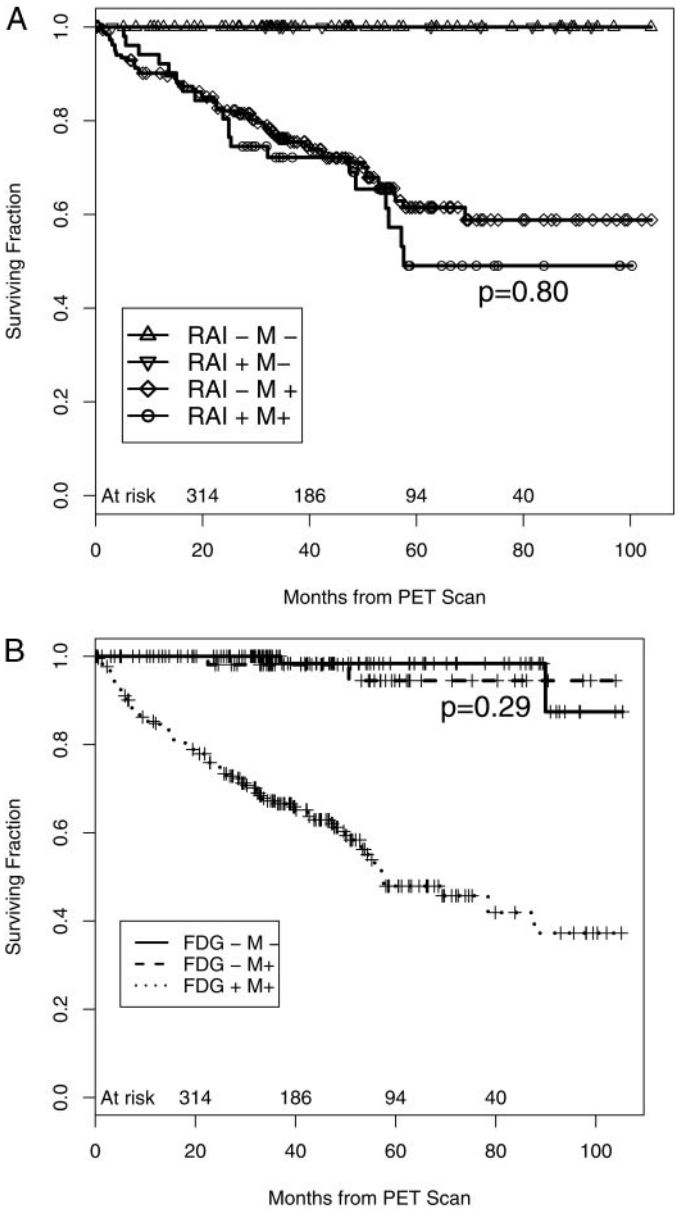


FIG. 5. Kaplan-Meier plot of survival of thyroid cancer patients with or without metastases. A, Interaction of effects of metastases and radioiodine avidity. The *lower two curves* are not statistically different ($P = 0.08$); B, Interaction of metastases and FDG avidity. The *upper two curves* are not statistically different ($P = 0.29$). M−, No evidence of metastasis; M+, presence of metastases; RAI−, negative radioiodine scan; RAI+, positive radioiodine scan; FDG+, abnormal uptake of FDG; FDG−, no abnormal uptake of FDG.

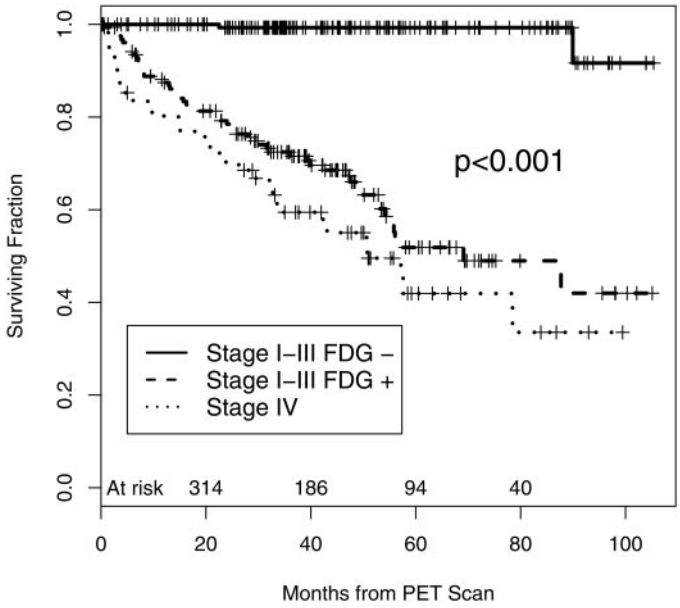


FIG. 6. Kaplan-Meier survival plots of thyroid cancer patients based on combined consideration of stage and FDG-PET scan result. Stage I-III includes all patients who had initial AJCC staging of I, II, or III. PET−, Negative FDG-PET scan; PET+, positive FDG-PET scan.

## Discussion

We performed this study to test the hypothesis that FDG-PET scan results could provide real-time prognostic information for patients with metastatic thyroid carcinoma. There is no evidence-based prognostic system that enables physicians to estimate survival in thyroid cancer patients at the time that metastases are subsequently discovered. Patients with metastatic thyroid cancer have been reported to survive for up to 30 yr (15). Conversely, some patients with distant metastases succumb within 1 yr. Other than anaplastic thyroid carcinoma, which is highly fatal, the histology of the original primary tumor alone seldom allows reliable prognostication. We hypothesized that the initial FDG scan would provide sufficient quantitative information to provide a context for the timing and intensity of therapeutic choices. Although serial FDG scans would likely provide a better trajectory of the disease, we have considered only the initial scan so as not to bias the data toward those patients who had multiple FDG scans.

Our results suggest that, in comparison with a number of other clinical, radiological (*e.g.* ultrasonography and chest x-rays), and biochemical markers, the FDG-PET scans provide anatomical as well as prognostic information. Although the patients who are referred to our medical center have more advanced disease, we feel that these results are relevant to any thyroid cancer survivor who has residual or recurrent metastatic disease. Patients in our cohort with a positive FDG scan had 7.28 times the risk of dying, compared with thyroid cancer survivors (with or without metastases; Fig. 5B) who had a negative FDG scan. Our Kaplan-Meier survival curves demonstrate that median survival for FDG-positive patients occurs at 53 months after the PET scan. This compares with only two deaths to date in this cohort from thyroid cancer in the 180 patients who had a negative FDG scan. Both the $SUV_{max}$ and the number of lesions are quantitative measures that are readily available from standard dedicated PET scanners, and they have strong predictive value. Another important variable to consider is the site of the metastatic lesion. We found that patients with FDG-avid local recurrences fare much better than those with FDG-avid distant metastases. Finally, although the TNM stage (based on data collected at initial diagnosis) correlated with survival on univariate analysis, it was not significant on multivariate analysis. In fact, our stage I-III patients with FDG-positive disease had a survival very similar to all of the stage IV patients.

Shoup *et al.* (8) recently reported on a separate group of thyroid cancer survivors (between 1941 and 2000) from Memorial Sloan-Kettering Cancer Center. They followed the progress of 336 thyroid cancer patients who had distant metastases. No FDG scans were reported in that cohort. After multivariate analysis, they found that age younger than 45 yr, lack of symptoms, metastases in lung only or bone only, and radioactive iodine treatment all conferred a significantly better prognosis. Interestingly, 26% of the patients were still alive at 10 yr of follow-up, in agreement with previous reports (16, 17). They also found that for patients younger than 45 yr of age at diagnosis, survival was longer in those who had distant metastases at the time of initial diagnosis, compared with those who developed metastases more than 6 months later. This difference was not apparent for those 45 yr of age or older.

In a large retrospective study of metastatic papillary thyroid cancer patients from the Mayo Clinic, overall survival was reported to be 20% at 15 yr (18). Using a multivariate Cox model, these investigators found that older age, extrathyroidal extension at initial surgery, and nonlung sites of distant metastases all carried significantly negative prognostic influences. In that report, those with radioiodine-avid distant metastases who received radioiodine therapy had significantly better survival than those whose tumors did not concentrate radioiodine. This outcome is consonant with the observation that well-differentiated metastases from thyroid cancer tend to concentrate radioiodine but not FDG, whereas poorly differentiated metastases exhibit the opposite pattern (19–21).

As in our study, younger age at the discovery of DM has been reported to be a strong independent favorable survival factor (7, 16, 22). It is well documented that certain patterns of DM disease have a more indolent course. These include micronodular lung metastases in younger individuals and isolated bone metastases that concentrate radioiodine (23).

Approximately 10 yr ago, FDG-PET scanning was studied as a means to locate occult residual thyroid cancer in patients with elevated serum Tgs and negative radioiodine whole-body scans (24, 25). It then became clear that the high metabolic activity revealed by FDG avidity implied poorly differentiated elements as evidenced by lack of iodine avidity. We published in support of this concept by showing that FDG-avid metastatic lesions are relatively resistant to high dose therapy with 131-I (26).

In our earlier preliminary report on the prognosis of patients with FDG-avid disease, we found that the volume of metastatic disease had the strongest influence of any variable on survival. Multivariate analysis also identified age at PET older than 45 yr, distant metastases, a positive FDG scan, and the $SUV_{max}$ as significant predictors of survival (9). Due to the complexity of determining FDG tumor volume, we have now eliminated this variable and substituted the number of FDG-avid lesions as a volume surrogate, which can be easily determined by nuclear medicine physicians trained in PET scanning. In this larger report, with longer follow-up, multivariate analysis shows that age at PET older than 45 yr and the FDG scan results continue to be strong predictors of survival. We found that both FDG quantitative outcomes, $SUV_{max}$ and number of lesions, were able to stratify the overall risk, and they each held up under multivariate analysis.

By its retrospective nature, our study has inherent biases. The fact that 50% of the patients in this study had metastases reflects the referral pattern to a tertiary cancer center. The patients who met our inclusion criteria were referred for FDG scans by many different physicians for a wide variety of reasons. Some of the patients who had scans in the first 2 yr had no evidence of metastatic disease and, at present, would not ordinarily be evaluated by an FDG scan. The optimal use of FDG scanning in the management of patients with thyroid cancer has not been defined. The U.S. government, however, has recently approved Medicare reimbursement for its use in thyroid cancer survivors who have a serum Tg above 10 ng/ml and a negative radioiodine whole-body scan to localize disease. FDG-PET scanning has matured from being a novel localization technique into an important prognostic tool for breast cancer (27), gastric cancer (28), brain tumors (29), and prostate cancer (30). Our results confirm that this pattern also holds for thyroid carcinoma.

There are reports showing that the retention of FDG in some metastatic lesions may be influenced by the TSH level (31). We previously reported on a similar phenomenon (20); however, in the current database, which examined only the standard uptake values of the hottest single lesion, we did not find a statistical difference between the $SUV_{max}$ in those with suppressed TSH levels and those with elevated TSH levels. This should not be misconstrued to suggest that the TSH level may not increase the FDG uptake of some lesions, only that it did not seem to affect FDG uptake in the most metabolically active lesions. Finally, it is well documented that FDG can abnormally accumulate in tissue due to nonmalignant processes such as inflammation, muscle tension, and infection. All clinicians must consider the possibility that a focus of FDG uptake might not represent a metastatic lesion, even in thyroid cancer patients who have metastatic disease, before making therapeutic decisions (20, 32).

In conclusion, we recommend that an FDG scan be considered for all thyroid cancer survivors who have a demonstrated or suspected metastatic lesion based on clinical findings, radiologic imaging, or an elevated serum Tg (a suppressed Tg of $> 10$ ng/ml). A negative FDG scan will reassure the patient that there is no imminent danger, whereas a positive scan should lead the physician and patient to consider options such as surgery or external radiation because FDG-avid lesions are seldom destroyed by radioiodine therapy alone (26).

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