

## <sup>18</sup>F-Fluorodeoxyglucose Positron Emission Tomography in the Management of Patients with Thymic Epithelial Tumors

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### Abstract

**Purpose:** There are limited data regarding the role of <sup>18</sup>F-fluorodeoxyglucose positron emission tomography (<sup>18</sup>F-FDG PET) imaging in management of patients with thymic epithelial tumors (TET). The primary objective of this study was to assess the usefulness of early <sup>18</sup>F-FDG PET to monitor treatment efficacy and its correlation with Response Evaluation Criteria in Solid Tumors (RECIST) in patients with TETs.

**Experimental Design:** <sup>18</sup>F-FDG PET/computed tomographic (CT) scans were conducted at baseline and after 6 weeks of treatment in patients enrolled in two phase II and one phase I/II clinical trials. On the basis of data from other solid tumors, metabolic response was defined as a reduction of <sup>18</sup>F-FDG uptake by more than 30% as assessed by average standardized uptake values (SUV) of up to five most metabolically active lesions.

**Results:** Fifty-six patients with unresectable Masaoka stage III or IV TETs were included. There was a close correlation between early metabolic response and subsequent best response using RECIST ( $P < 0.0001$ – $0.0003$ ); sensitivity and specificity for prediction of best response were 95% and 100%, respectively. Metabolic responders had significantly longer progression-free survival (median, 11.5 vs. 4.6 months;  $P = 0.044$ ) and a trend toward longer overall survival (median, 31.8 vs. 18.4 months;  $P = 0.14$ ) than nonresponders. <sup>18</sup>F-FDG uptake was significantly higher in thymic carcinoma than in thymoma ( $P = 0.0004$ – $0.0010$ ).

**Conclusion:** In patients with advanced TETs, early metabolic response closely correlates with outcome of therapy. <sup>18</sup>F-FDG PET may be used to monitor treatment efficacy and assess histologic differences in patients with advanced TETs. *Clin Cancer Res*; 19(6); 1487–93. ©2013 AACR.

### Introduction

Thymic epithelial tumors (TET) are the most common malignancies of the anterior mediastinum (1). On the basis of morphology and atypia of the neoplastic epithelial cells and their relative proportion compared with lymphocytes, the World Health Organization (WHO) classification groups TETs into a continuum of tumors with increasing degrees of aggressiveness: from type A, AB, B1, B2, and B3 to type C (thymic carcinoma; ref. 2). The WHO classification along with the Masaoka staging system, which is based on

the integrity of the thymic capsule, degree of local tumor invasion, and presence of distant metastases (3), is used to predict the biologic behavior and prognosis of TETs (4, 5).

Types A, AB, and B1 thymoma have an excellent overall survival rate of more than 90% to 95% at 10 years (6). Five-year survival rates for types B2, B3, and thymic carcinoma are 75%, 70%, and 48%, respectively. Thymic carcinomas account for less than 1% of TETs and display a more aggressive phenotype with higher likelihood of distant metastases than in thymomas (7).

Commonly used methods for response assessment using computed tomography (CT) and the Response Evaluation Criteria in Solid Tumors (RECIST) have several limitations in the evaluation of TETs (8). Functional response assessment using positron emission tomography (PET) scans with <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) has been widely used in the diagnosis, staging, and prediction of response of many solid tumors (9, 10). Such assessments could provide an early, yet accurate, assessment of the response to a multicourse therapy and could facilitate therapy modifications. However, given the low incidence of TETs, the use of PET in these malignancies is not well-defined, and few clinical studies with <sup>18</sup>F-FDG PET have been conducted.

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (<http://clincancerres.aacrjournals.org/>).

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doi: 10.1158/1078-0432.CCR-12-2929

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### Translational Relevance

Limited data exist regarding the role of  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ -FDG PET) in monitoring treatment and predicting outcomes in thymic epithelial tumors (TET). Studies in this area have been retrospective and have involved small sample sizes and inconsistent measures of  $^{18}\text{F}$ -FDG uptake. In this retrospective analysis of prospectively collected data, we found that effective treatment with chemotherapy or targeted therapy causes rapid reduction in  $^{18}\text{F}$ -FDG uptake in patients with advanced or recurrent TETs. We also observed that early metabolic response predicts eventual Response Evaluation Criteria in Solid Tumors (RECIST) response and is associated with improved progression-free survival. The use of an early assessment of metabolic response to treatment could be translated to clinical practice wherein patients who do not achieve an early metabolic response could be switched to alternative therapeutic approaches.

This study is a retrospective analysis of prospectively collected data, primarily aimed to assess the usefulness of early  $^{18}\text{F}$ -FDG PET to monitor treatment efficacy and its correlation with anatomic imaging-based response assessment. Other objectives were to evaluate the use of baseline  $^{18}\text{F}$ -FDG PET and early metabolic response to treatment as predictors of survival and the association between  $^{18}\text{F}$ -FDG PET assessment and histology.

### Materials and Methods

#### Patients

As part of the clinical protocols, whole-body  $^{18}\text{F}$ -FDG PET/CT scans were conducted at baseline and early post-treatment in 56 consecutive patients with histologically confirmed, unresectable advanced (Masaoka stage III or stage IV) TETs enrolled in clinical trials at the National Cancer Institute (NCI) between December 2007 and October 2011. Patients had no major surgery, radiation, chemotherapy, and biologic or hormonal therapies within 4 weeks before study entry or between imaging sessions. Glucose levels within acceptable limits were reported in all patients without significant changes between  $^{18}\text{F}$ -FDG PET imaging sessions. All patients had measurable disease, which had a minimum diameter of  $>10$  mm on helical CT scan. Following initial WHO pathologic classification, patients with thymoma were stratified into 2 risk groups: low-risk (types A, AB, and B1) and high-risk (types B2 and B3; refs. 2, 11). All patients gave written informed consent in accordance with the NCI Institutional Review Board regulations.

#### Treatment

Patients who were previously treated for advanced disease with at least one platinum-based chemotherapy were treated

with cixutumumab, an insulin-like growth factor receptor 1 (IGF1R) inhibitor (NCT00965250; ref. 12) or belinostat, an histone deacetylase (HDAC) inhibitor (NCT00589290) (13). Treatment was continued until disease progression or development of unacceptable toxicities. Patients untreated for advanced disease received belinostat, with cisplatin, doxorubicin, and cyclophosphamide (PAC; NCT01100944) for up to 6 cycles or until disease progression (14).

#### $^{18}\text{F}$ -FDG PET imaging and analysis

Baseline and early posttreatment  $^{18}\text{F}$ -FDG PET/CT were obtained within 28 days before starting treatment and at 6 weeks ( $\pm 4.0$  days) after starting treatment, respectively.  $^{18}\text{F}$ -FDG PET/CT findings were considered exploratory and not used for treatment decisions. Methodologic details of  $^{18}\text{F}$ -FDG PET/CT image acquisition and analysis are provided in Supplementary Appendix A.

We calculated 4 estimates of  $^{18}\text{F}$ -FDG uptake for baseline and follow-up PET scans: (i) maximum standardized uptake values ( $\text{SUV}_{\text{max}}$ ) of the single most metabolically active lesion, (ii) average  $\text{SUV}_{\text{max}}$  of up to 5 most metabolically active lesions ( $\text{SUV}_{\text{average}}$ ), (iii) ratio of  $\text{SUV}_{\text{max}}$  of most metabolically active lesion to the mean SUV of the mediastinum ( $T/M_{\text{max}}$ ), and (iv) ratio of average  $\text{SUV}_{\text{max}}$  of up to 5 most metabolically active lesions to the mean SUV of the mediastinum ( $T/M_{\text{average}}$ ).

#### Response evaluation and follow-up

Contrast-enhanced helical CT scans of chest, abdomen, and pelvis were obtained at baseline and every 6 weeks to evaluate tumor response based on the RECIST guidelines (15). Patients were followed up yearly for survival status. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression or death (whichever occurred first). Overall survival (OS) was defined as the time from treatment initiation until death resulting from any cause. For analysis of changes in  $^{18}\text{F}$ -FDG uptake between baseline and early posttreatment scans, the starting times for PFS and OS were the time of the follow-up scan.

#### Statistical analysis

The primary objective of this study was to assess the usefulness of early  $^{18}\text{F}$ -FDG PET to monitor treatment efficacy and its correlation with anatomic imaging-based response assessment. Metabolic response was defined as a decrease of baseline  $\text{SUV}_{\text{average}}$  by more than 30%, based on established guidelines (9). Lack of metabolic response was defined by an increase of  $\text{SUV}_{\text{average}}$  or decline from baseline of less than 30%.

Two-group comparisons of quantitative outcomes were made using the exact Wilcoxon rank-sum test, and comparisons of 3 or more categorical factors using the exact Kruskal-Wallis test. Trends in the outcomes across ordered groups were assessed using the exact Jonckheere-Terpstra test (16). Histology distributions and response rates over the treatment groups were tested by

the Fisher-Freeman-Halton method (17). The diagnostic accuracy of changes in PET parameters to predict subsequent response was compared by receiver-operating characteristic (ROC) curves. Estimation of PFS and OS was conducted by the Kaplan-Meier method, and the log-rank test of the proportional hazards model was applied to test possible associations with them. Results are from SAS version 9.3 statistical software (SAS Institute Inc.).

**Results**

**Patient characteristics and [<sup>18</sup>F]-FDG PET analysis**

Between December 2007 and October 2011, 56 patients were evaluated. Patient characteristics are listed in Table 1. Thymic carcinoma accounted for 39% of cases. Low- and high-risk groups accounted for 26% and 67% of patients with thymoma, respectively. Eighty-seven percent of patients had received prior chemotherapy. The distribution of histologies in the 3 treatment groups was comparable: 65%, 57%, and 60% of patients had thymoma in the cixutumumab, belinostat, and PAC/belinostat trials, respectively.

All 56 patients underwent baseline imaging and had abnormal <sup>18</sup>F-FDG uptake defined as having at least one lesion with an SUV of more than 2.5 (18). The number of lesions assessed in each patient ranged from 1 to 5 (mean, 3.8 ± 1.1). All 4 of the baseline [<sup>18</sup>F]-FDG-PET measurements showed no association with the number of lesions assessed (*P* > 0.40), which showed that the number of lesions could be disregarded in all analyses involving the measurements. Early posttreatment [<sup>18</sup>F]-FDG PET was conducted in 48 (86%) patients.

**[<sup>18</sup>F]-FDG PET to monitor treatment efficacy**

Objective response rate [ORR; complete response (CR) + partial response (PR)] in the entire study group was 18%: 26% for thymoma (PR, 8; CR, 1) and 5% for thymic carcinoma (PR, 1). Among the responders for whom baseline and early posttreatment [<sup>18</sup>F]-FDG PET were available, the duration of treatment before RECIST responses were variable (range, 2–10 cycles; median, 2). Table 2 shows quantitative measures of metabolic activity and overall best response according to RECIST. The relative change in metabolic activity from baseline to early posttreatment [<sup>18</sup>F]-FDG PET predicted the subsequent best response by RECIST (*P* = <0.0001–0.0003; Table 2). Moreover, lower early posttreatment metabolic activity was associated with a higher likelihood of subsequent tumor response (*P* = 0.0012–0.0037).

The established threshold of 30% for SUV<sub>average</sub> identified patients with eventual RECIST stable or progressive disease with a sensitivity and specificity of 95% and 100%, respectively (Table 3). A higher proportion of patients treated with PAC/belinostat had a metabolic response compared with cixutumumab or belinostat: 6 of 9 (67%) versus 2 of 18 (11%) versus 1 of 21 (5%), respectively (*P* = 0.0003). Furthermore, we estimated optimal threshold which were observed to have the highest sensitivity and specificity for

**Table 1.** Patient characteristics (*N* = 56)

Variable	No. (%)
Age, y	
Median (range)	52 (26–86)
Gender	
Male	30 (54)
Female	26 (46)
Ethnicity	
Caucasian	38 (68)
African American	8 (14)
Asian	8 (14)
Hispanic	2 (4)
Histologic group	
Thymoma	34 (61)
AB	4
B1	5
B2	15
B3	8
Uncategorized	2
Thymic carcinoma	22 (39)
Stage at presentation	
III unresectable	1 (2)
IVA	13 (23)
IVB	42 (75)
Time from diagnosis, median (range), mo	
Thymoma	61.5 (1–150)
Thymic carcinoma	24 (1–48)
Number of patients in each clinical protocol	
Cixutumumab	23 (41)
Belinostat	23 (41)
PAC/belinostat	10 (18)
Prior therapy	
Prior therapy for advanced TET	46 (82)
No prior therapy	7 (13)
Prior adjuvant/neoadjuvant therapy	3 (5)
Prior surgical resection of primary tumor	
Yes	31 (55)
No	25 (45)
Prior radiation therapy	
Yes	29 (52)
No	27 (48)

Abbreviations: *N*, number of patients; PAC, cisplatin/adriamycin/cyclophosphamide.

RECIST response in this data set. All patients who had eventual responses to treatment by RECIST had decreases of 35% or more in the SUV<sub>average</sub>, whereas only one of the nonresponders had a decrease in this range. Using the optimal threshold, the estimated sensitivity and specificity in detecting stable or progressive disease were 97.5% and 100%, respectively (Fig. 1: area under ROC curve = 0.98). Figure 2 shows representative PET/CT images of responding and nonresponding tumors.

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**Table 2.** Quantitative measures of metabolic activity and overall best response by RECIST

Measure of metabolic activity	CR (N = 1)	PR (N = 7)	SD (N = 31)	PD (N = 9)	P
Median % change in SUV between baseline and early post treatment <sup>18</sup> F-FDG PET scans					
SUV <sub>max</sub>	-32	-64	7	11	0.0003
SUV <sub>average</sub>	-51	-44	0	6	<0.0001
T/M <sub>max</sub>	-54	-67	2	7	0.0001
T/M <sub>average</sub>	-67	-48	-4	15	<0.0001
Median early posttreatment SUV					
SUV <sub>max</sub>	4.9	2.8	7.6	8.0	0.0013
SUV <sub>average</sub>	2.7	3.3	5.9	6.6	0.0032
T/M <sub>max</sub>	2.0	1.8	4.6	5.5	0.0012
T/M <sub>average</sub>	1.1	2.0	3.6	4.7	0.0037

NOTE: Response evaluated using dedicated computed tomography scans according to the RECIST version 1.1. Abbreviations: N, number of patients; PD, progressive disease; SD, stable disease.

### Metabolic response and survival

The estimated median follow-up time was 20.9 months (range, 1.4–48.6) for all patients, 19.3 (1.4–48.6) for patients with thymoma, and 20.9 (4.3–20.9) for patients with thymic carcinoma. Tumor progression occurred in 30 (88%) patients with thymoma and 21 (95%) patients with thymic carcinoma. Deaths occurred in 11 (32%) patients with thymoma and 18 (82%) patients with thymic carcinoma during the follow-up interval. The median PFS and OS were 5.9 and 19.8 months, respectively. Patients with thymic carcinoma had inferior PFS and OS (median PFS and OS, 2.7 and 12.2 months) compared with patients with thymoma (7.8 and 35 months;  $P < 0.0001$  for each). There was no difference in PFS or OS between high- and low-risk groups of thymoma (results not shown).

Compared with nonresponders, metabolic responders had an increased PFS (median, 11.5 vs. 4.6 months,  $P = 0.044$ ) and a trend toward improved OS (median, 31.8 vs. 18.4 months,  $P = 0.14$ ) using the established SUV<sub>average</sub> threshold of 30% (Fig. 3). Similar results were observed using the optimal SUV<sub>average</sub> threshold of 35% (median PFS, 11.5 vs. 4.4 months,  $P = 0.024$ ; median OS, 31.8 vs. 16.5 months,  $P = 0.062$ ). In the proportional hazards model for PFS including both metabolic response and treatment

received as risk factors, treatment was found to have a nonsignificant  $P$  value, and the association of metabolic response with PFS remained strong (results not shown).

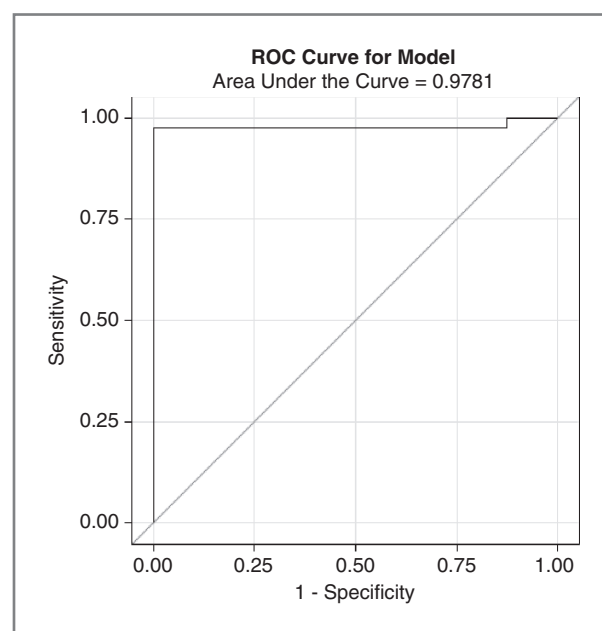
### [<sup>18</sup>F]-FDG PET and histology

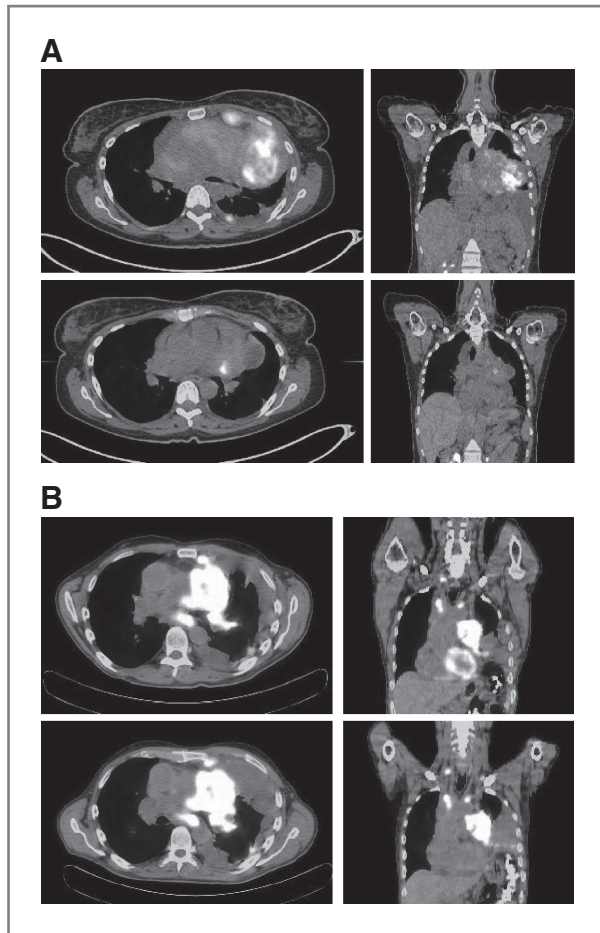
Table 4 shows quantitative measures of metabolic activity at baseline in the histologic subgroups. All estimates of baseline [<sup>18</sup>F]-FDG uptake were significantly higher in the thymic carcinoma than in thymoma ( $P = 0.0004$ – $0.0010$ ). Within the thymoma risk groups, high-risk thymoma had [<sup>18</sup>F]-FDG uptake similar to low-risk thymoma ( $P > 0.40$ ). A strong association was also found between early posttreatment [<sup>18</sup>F]-FDG uptake and histology (results not shown).

**Table 3.** Metabolic response using the established threshold and overall best response by RECIST

	RECIST best response		
	SD, PD	CR, PR	Total
SUV <sub>average</sub> change > -30%	38	0	38
SUV <sub>average</sub> change < -30%	2	8	10
Total	40	8	48

Abbreviations: PD, progressive disease; SD, stable disease.

**Figure 1.** ROC curves showing discrimination between responders and nonresponders using SUV<sub>average</sub>.

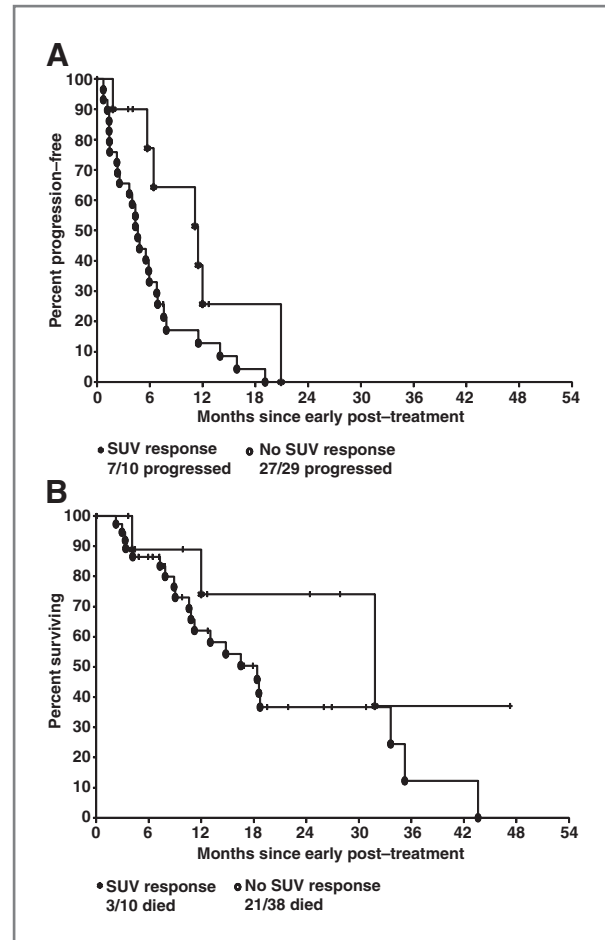


**Figure 2.** Black and white [<sup>18</sup>F]-FDG PET/CT images of a responding (A) and nonresponding (B) tumor. A, [<sup>18</sup>F]-FDG PET/CT images of a 41-year-old female with type B2 thymoma at baseline (top row) and at 6 weeks (bottom row) after initiation of belinostat, with cisplatin, doxorubicin, and cyclophosphamide. The images in axial and coronal planes show decrease in tumor size and decline of SUV<sub>max</sub> by 74%. B, [<sup>18</sup>F]-FDG PET/CT images of a 58-year-old male with thymic carcinoma at baseline (top row) and at 6 weeks (bottom row) after initiation of cixutumumab. The images in axial and coronal planes show increased FDG uptake in left subpleural masses and stable uptake in a large mediastinal mass and lymph nodes.

Survival analyses conducted separately for the 2 histologic subgroups and after stratifying for histology showed no association between baseline [<sup>18</sup>F]-FDG uptake and OS or PFS ( $P > 0.55$  for each). Early posttreatment [<sup>18</sup>F]-FDG uptake and change in uptake between baseline and early posttreatment also had no association with OS or PFS ( $P > 0.50$ ).

## Discussion

Despite the growing use of [<sup>18</sup>F]-FDG PET imaging in oncology (9, 10), limited data exist regarding its use in monitoring treatment response and predicting survival in advanced TETs (11, 19–31). With a few exceptions (25, 27, 28, 30), most studies in this area have been retrospective, involving small sample sizes and inconsistent



**Figure 3.** Kaplan–Meier plots of PFS (A) and OS (B) of metabolic responders (defined as a decline of 30% or more in SUV<sub>average</sub>) and nonresponders.

measures of [<sup>18</sup>F]-FDG uptake. Furthermore, the majority of the studies have an overrepresentation of thymoma compared with thymic carcinoma. There is limited information on its role in monitoring treatment response and as a predictor of survival (20, 23), and we are not aware of prospective systematic studies addressing these questions.

As a retrospective analysis of prospectively collected data, this study shows that in patients with advanced or recurrent TETs: (i) effective treatment with chemotherapy or targeted therapy causes rapid reduction in [<sup>18</sup>F]-FDG uptake, (ii) early metabolic response predicts eventual RECIST response and is associated with improved PFS, and (iii) baseline [<sup>18</sup>F]-FDG uptake correlates well with histology but is not a predictor of survival after adjusting for histology and cannot differentiate between high- and low-risk thymoma.

We observed rapid and significant reductions in metabolic activity with effective treatment in TETs. In contrast, no significant decrease in metabolic activity was seen with treatment that was ineffective. For all estimates of [<sup>18</sup>F]-FDG uptake, the relative decline in [<sup>18</sup>F]-FDG uptake with treatment and a lower early posttreatment metabolic activity were associated with higher likelihood of subsequent

**Table 4.** Quantitative measures of metabolic activity at baseline in the histologic subgroups

Measure of metabolic activity	Thymoma (N = 34) median	Thymic carcinoma (N = 22) Median	P	Low-risk thymoma (N = 9) median	High-risk thymoma (N = 23) median	Thymic carcinoma (N = 22) median	P
SUV <sub>max</sub>	5.8	9.5	0.0010	6.0	5.7	9.5	0.0050
SUV <sub>average</sub>	4.9	7.5	0.0005	5.3	4.3	7.5	0.0015
T/M <sub>max</sub>	3.6	6.8	0.0004	3.8	3.6	6.8	0.0029
T/M <sub>average</sub>	2.9	4.8	0.0007	3.5	2.9	4.8	0.0036

Abbreviation: N, number of patients.

RECIST response. Our results suggest the use of [<sup>18</sup>F]-FDG PET use in monitoring response to treatment in advanced TETs. These results are consistent with observations in several malignancies including breast, esophageal, and gastric cancers that early metabolic response to chemotherapy or targeted agents correlated well with the eventual RECIST response (32–34). Decreases in T/M from baseline have been previously reported in a retrospective analysis of 4 patients with advanced TETs and RECIST partial responses (20). This study, however, was limited by the small number of patients ( $n = 12$ ) and heterogeneity in histology (10 thymic carcinoma, 2 thymoma) and treatment (10 systemic therapy, 2 radiotherapy).

In solid tumors, a decline of metabolic activity of 30% or more with treatment is thought to represent a medically relevant beneficial change (9). However, in TETs, there is no uniformly accepted treatment metabolic response metrics. Using the established SUV<sub>average</sub> threshold of 30%, we predicted eventual nonresponders with a sensitivity and specificity exceeding 95%. On the basis of highest sensitivity and specificity to predict RECIST responses, we also identified an optimal SUV<sub>average</sub> threshold (35%) to identify metabolic response from our dataset. Notably, the optimal threshold identified for our dataset and the established threshold were remarkably close to each other. Moreover, independent of the treatment, metabolic responders identified using both thresholds had significantly improved PFS and a trend toward improved OS, compared with nonresponders. Similar correlations between metabolic response to treatment and improved patient outcomes have been reported in several other malignancies (10).

After adjusting for histologic differences, we found no association between tumor metabolic activity and survival. However, consistent with previous reports, our study found higher [<sup>18</sup>F]-FDG uptake in thymic carcinoma than in thymoma (11, 22, 23, 28, 29), although there were no significant differences in uptake among the high- and low-risk groups of thymoma. Previous studies have found discordant results on [<sup>18</sup>F]-FDG uptake among the thymoma risk groups. Whereas some investigators reported the usefulness of [<sup>18</sup>F]-FDG PET/CT (11, 23, 24, 28, 30), a marked overlap in uptake among high- and low-risk thymomas was also observed (27, 29). Probable contributing factors to the wide range of reported associations include small number

of patients in prior reports, difficulties in histologic classification of thymomas and inconsistent definitions of risk groups (19, 21, 24, 26).

In this study, we show the use of [<sup>18</sup>F]-FDG PET to monitor treatment efficacy and assess histologic differences in patients with advanced or recurrent TETs. In addition to being the largest series of prospectively collected [<sup>18</sup>F]-FDG PET data, the strengths of our study include a uniform patient population, all having advanced TETs and receiving systemic therapy, even representation of all the major histologic groups, availability of long-term follow-up data, and multiparameter assessment of metabolic changes. Although early assessment of response to treatment can be potentially useful, for example, to discontinue an ineffective treatment, it is not yet clear whether it can alter treatment and result in beneficial effects on patient outcomes. Further studies are needed to clarify the role of [<sup>18</sup>F]-FDG PET in patients with TETs in other clinical settings. For example, using [<sup>18</sup>F]-FDG PET imaging for detection of residual tumor after primary therapy or earlier detection of recurrence in asymptomatic patients may improve outcomes. Achieving new imaging benchmarks in patients with TETs also requires establishment of [<sup>18</sup>F]-FDG PET protocols that include standardized methods for uptake measurements and thresholds of response.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** A. Thomas, S. Khozin, A. Rajan, G. Giaccone  
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**Writing, review, and/or revision of the manuscript:** A. Thomas, E. Mena, K. Kurdziel, D. Venzon, S. Khozin, P. Choyke, E. Szabo, A. Rajan, G. Giaccone  
**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** A. Thomas, G. Giaccone  
**Study supervision:** A. Thomas, A.W. Berman, G. Giaccone

#### Grant Support

The study was supported by Intramural Program, National Cancer Institute, NIH.

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Received September 11, 2012; revised December 18, 2012; accepted January 15, 2013; published OnlineFirst February 4, 2013.

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