PRELIMINARY COMMUNICATION

Association of Posttherapy Positron Emission Tomography With Tumor Response and Survival in Cervical Carcinoma

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Context Retrospective studies have demonstrated that the use of positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) in the posttherapy evaluation of patients with cervical carcinoma is predictive of survival outcome.

Objective To validate the association between the metabolic response on the 3-month posttherapy FDG-PET and long-term survival outcome.

Design, Setting, and Patients A prospective cohort study designed to validate our previous finding that the results of a 3-month posttherapy FDG-PET are predictive of long-term clinical outcome. A total of 92 women were treated with external irradiation, brachytherapy, and concurrent chemotherapy from January 2003 through September 2006. Posttherapy whole-body FDG-PET was performed 2 to 4 months (mean, 3 months) after completion of therapy.

Main Outcome Measures The primary outcome end points were metabolic response, progression-free survival, and cause-specific survival.

Results Posttherapy FDG-PET showed a complete metabolic response in 65 patients (70%), a partial metabolic response in 15 (16%), and progressive disease in 12 (13%). Their 3-year progression-free survival rates were 78%, 33%, and 0%, respectively ($P < .001$). Multivariate analysis demonstrated that the hazard ratio (HR) for risk of recurrence based on the posttherapy metabolic response showing progressive disease was 32.57 (95% confidence interval [CI], 10.22-103.82). A partial metabolic response had an HR of 6.30 (95% CI, 2.73-14.56). These were more predictive of survival outcome than the pretreatment lymph node status (HR, 3.54; 95% CI, 1.54-8.09).

Conclusion In this single-site study population of women with cervical cancer, 3-month posttherapy FDG uptake, as detected by whole-body PET, was predictive of survival.

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CERVICAL CANCER RANKS AMONG the top 3 cancer diagnoses in women worldwide.[1] In the United States, the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review identified cervical cancer as the third leading cause (following childhood cancers and testicular cancer) of average years of life lost per person dying of cancer for all races and both sexes.[2] Recent strategies to reduce the incidence of cervical cancer have focused on the development of the human papilloma virus (HPV) vaccine. While the HPV vaccine has the potential to significantly reduce de novo HPV infection in women younger than 26 years, a significant population of women (>26 years of age and unvaccinated) is currently at risk for future development of cervical cancer. Even assuming 100% compliance with vaccination, a recent study estimated that the impact of HPV vaccination would not be appreciated clinically until after 2040.[3] In the coming years, clinicians will continue to face the challenges associated with the treatment and follow-up of patients with cervical cancer.

Approximately one-third of patients with cervical cancer develop disease recurrence and the majority of these recurrences occur within the first 2 years after completion of therapy.[4] Predictors of disease recurrence include stage and lymph node status at the time of initial diagnosis.[5,6] In addition, persistent cervical tumor on clinical examination performed 1 to 3 months after completion of therapy is associated with an increased risk of recurrence and poor overall survival.[7] Recent reports suggest that the early detection of recurrences may positively affect clinical outcome for selected patients.[8,9] These data emphasize the importance of clinical follow-up for patients with cervical cancer, particularly in the immediate posttherapy period.

Current recommendations for the posttherapy evaluation of patients treated

See also Patient Page.

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for cervical cancer include symptom evaluation and physical examination followed by serial pelvic examinations with cervical cytology (Papanicolaou test) beginning 3 months after the completion of therapy.[10] This strategy does not address initial response to treatment or early detection of disease recurrence. In addition, screening Papanicolaou tests are of limited utility in the posttherapy setting because of radiation-related pathological effects.[11-13]

We designed the current study to investigate the use of metabolic imaging in the follow-up of patients treated for advanced cervical cancer. Positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) has been used in the pretreatment and posttreatment evaluation of a variety of cancers, and is currently recommended by the National Comprehensive Cancer Network as part of the pretreatment assessment for patients with cervical cancer of clinical stage Ib2 or higher.[10] We have reported our initial experience with the use of FDG-PET in the posttherapy setting.[14] The current study extends the follow-up of the use of FDG-PET in the initial cohort and includes validation in a subsequent prospective cohort in the routine follow-up of patients treated for cervical cancer.

METHODS

Patients

Patients were treated at Washington University for cervical cancer between March 1998 and September 1, 2006. The treatment regimens, follow-up, and imaging studies were similar for all patients. Patients provided written informed consent. Approval from the institutional review board (Washington University Human Research Protection Office) was obtained for this study.

Initial Cohort

The characteristics of the 152 patients involved in the retrospective data set were reported previously.[14] Briefly, these patients were diagnosed with cervical cancer from March 1, 1998, through December 31, 2002, and underwent concurrent chemoradiation therapy. For this study, we include additional follow-up data for the retrospective cohort through December 31, 2006. The mean follow-up was extended from 28 to 70 months. At time of last follow-up, 86 patients had no evidence of disease, 6 patients were alive with disease, 51 patients died of disease, and 9 died of causes other than cervical cancer.

Prospective Cohort

For the prospective portion of this study, patients diagnosed with cervical cancer from January 1, 2003, through September 1, 2006, were entered into a tumor registry. Both pretreatment and posttreatment FDG-PET/computed tomography (CT) imaging studies were obtained as part of standard clinical practice at our institution. Patients in this report completed concurrent chemoradiation treatment (see below). All patients must have presented for follow-up FDG-PET/CT between 8 and 16 weeks (mean, 12.5 weeks) after the completion of therapy and completed at least 6 months of clinical follow-up. Patients treated with palliative therapy and those undergoing follow-up FDG-PET/CT outside the 8- to 16-week window were excluded.

The study population included 92 total patients. Their ages ranged from 24 to 83 years (mean, 51 years). Tumor histology was squamous cell carcinoma in 81 patients, adenocarcinoma in 7 patients, adenosquamous carcinoma in 1 patient, and clear cell carcinoma in 3 patients.

There were 13 patients with International Federation of Gynecology and Obstetrics stage Ib1 disease, 14 with stage 1b2, 2 with stage IIa, 42 with stage IIb, 1 with stage IIIa, 18 with stage IIIb, and 2 with stage IVa.

Radiotherapy for cervical cancer was performed in all patients and consisted of external irradiation and intracavitary brachytherapy. The mean total radiation dose to point A was 82.1 Gy. Concurrent chemotherapy (6 weekly cycles of 40 mg/m^2 of cisplatin) was administered to all patients.

Duration of follow-up ranged from 6 to 49 months (mean, 25 months). At the time of last follow-up, December 31, 2006, 61 patients had no evidence of disease, 18 patients were alive with disease, 12 patients died of disease, and 1 patient died from causes other than cervical cancer.

Clinical Follow-up

Clinical follow-up of patients was performed 6 weeks after the completion of therapy and periodically as follows: monthly for 3 months, every 3 months until 12 months, every 4 months for the second year, and every 6 months during years 3 to 5. Follow-up imaging studies consisted of CT and/or FDG-PET/CT as clinically indicated. No specific imaging schedule was implemented initially but in the later years of this study FDG-PET/CT generally was performed on a 6- to 12-monthly basis. Recurrences were biopsy proven in more than 50% of the cases of recurrent disease; and in the remainder of cases, recurrences were proved by monthly follow-up with documentation of disease progression.

FDG-PET Imaging

Before November 2002, FDG-PET was performed using a conventional PET scanner and interpreted as previously described.[15] Thereafter, all FDG-PET studies were performed with a hybrid PET/CT scanner using methods described by Wright et al.[16] PET studies were deferred if the blood glucose concentration exceeded 200 mg/dL (to convert to mmol/L, multiply by 0.0555). PET/CT images were interpreted in a standard clinical fashion, both separately and in a fused mode. Pretreatment lymph node status was determined from the diagnostic FDG-PET study. A complete metabolic response was defined as absence of abnormal FDG uptake at sites of abnormal FDG uptake noted on the pretreatment FDG-PET study. A partial response was defined as any persistent abnormal FDG uptake at these sites. New foci of abnormal FDG uptake also were noted.

Statistical Analysis

Metabolic response, progression-free survival, and cause-specific survival were the major end points of this study. Survival and tumor recurrence were measured from the completion of treatment. Stat-

View version 5.0.1 software (SAS Institute Inc, Cary, North Carolina) was used for the analysis. $P < .05$ was set as the threshold for significance for all study outcomes. The Kaplan-Meier (product-limit) method was used to derive estimates of survival based on total sample size.[17] Tests of equivalence of estimates of survival were performed by the generalized Wilcoxon log-rank test.[18] Multivariate analysis was performed using the Cox proportional hazards regression model.[19]

The initial patient cohort consisted of 152 patients. The original analysis[14] of the cohort indicated that by multivariate proportional hazards modeling, the status of the 3-month posttherapy FDG-PET was the only independently significant prognostic factor for survival. That model was used to calculate the sample size of the prospective cohort. The sample size required to detect a 10% difference in progression-free survival at 3 years with an 80% power at a 2-sided α level of .05 was 90 patients. For the prospective cohort, a multivariate proportional hazards model of survival outcome was performed as a forward stepwise procedure using a *P*-to-enter value and a *P*-to-remove value of .05. The assumption of proportionality was tested and met. The time-dependent outcome variables were disease progression and survival. Variables initially tested in the model included tumor and treatment-related factors believed to be of significance in this population of patients with advanced stage cervical cancer. The variables entered into the first model were clinical stage, pretreatment lymph node status, total radiation treatment time, and number of cycles of chemotherapy as predictors of disease progression and survival. The forward stepwise procedure using a *P*-to-enter value and a *P*-to-remove value of .05 failed to allow total radiation treatment time and number of cycles of chemotherapy into the model (data not shown).

The next multivariate proportional hazards model was constructed using the remaining variables of clinical stage and pretreatment lymph node status. The variables of posttherapy FDG response, progressive disease, and partial metabolic response were added to this second model. The forward stepwise procedure using a *P*-to-enter value and a *P*-to-remove value of .05 failed to allow clinical stage to remain in the model. The final model that was constructed consisted of the variables: (1) lymph node status from the pretreatment FDG-PET and (2) progressive disease and partial metabolic response from the posttreatment FDG-PET.

Table 1. Baseline Characteristics

	No. (%) of Patients[a]	
	Initial Cohort (n = 152)	Prospective Cohort (n = 92)
Age, median (IQR), y	49 (41-57)	51 (42-60)
Clinical stage		
Ib1	17 (11)	13 (14)
Ib2	35 (23)	14 (15)
IIa	4 (3)	2 (2)
IIb	52 (34)	42 (46)
IIIa	2 (1)	1 (1)
IIIb	40 (26)	18 (20)
IVa	2 (1)	2 (2)
PET lymph node status		
None	48 (32)	48 (52)
Pelvic	81 (53)	30 (33)
Pelvic and para-aortic	23 (15)	14 (15)
Tumor histology		
Squamous	141 (93)	81 (88)
Adenocarcinoma	4 (3)	7 (8)
Adenosquamous	6 (4)	1 (1)
Clear cell	1 (1)	3 (3)

Abbreviations: IQR, interquartile range; PET, positron emission tomography.
[a] Unless otherwise indicated.

RESULTS

Initial Cohort

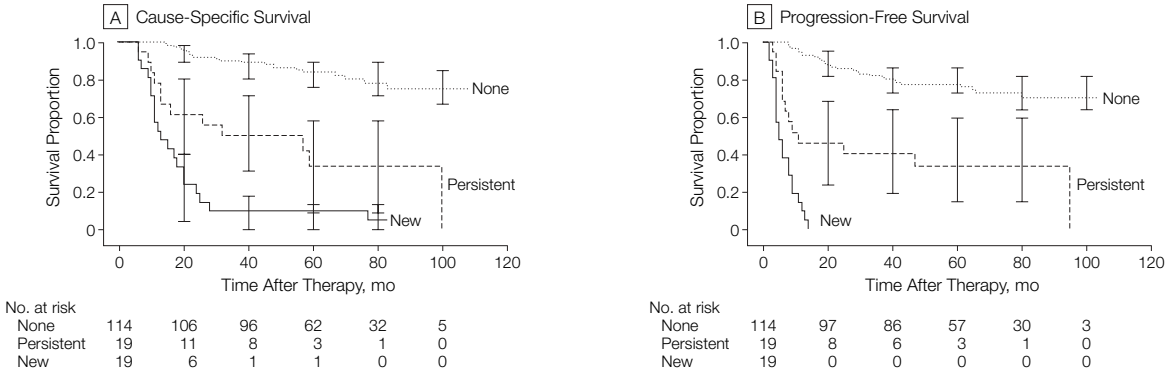
In the original patient data set (n = 152 patients), posttherapy PET showed a complete metabolic response in 114 patients (75%) (TABLE 1). There was persistent abnormal FDG uptake in the irradiated region (cervix/lymph nodes) in 19 patients (12.5%). New anatomic sites of FDG uptake outside of the irradiated region occurred in 19 patients (12.5%). The updated cause-specific survival by site of posttherapy FDG uptake is shown in FIGURE 1A. The 5-year cause-specific survival rates were 84% for those patients with a complete metabolic response on the posttherapy FDG-PET, 33% for those patients with persistent FDG uptake in the irradiated region, and 10% for those with new sites of FDG uptake outside of the initial irradiated region ($P < .001$).

Figure 1B demonstrates the corresponding 5-year progression-free survival rates. The 5-year progression-free survival rates were 77% for those patients with no abnormal FDG uptake on follow-up FDG-PET, 34% for those patients with persistent FDG uptake in the irradiated region, and 0% for those with new sites of FDG uptake outside of the initial irradiated region ($P < .001$).

Prospective Cohort

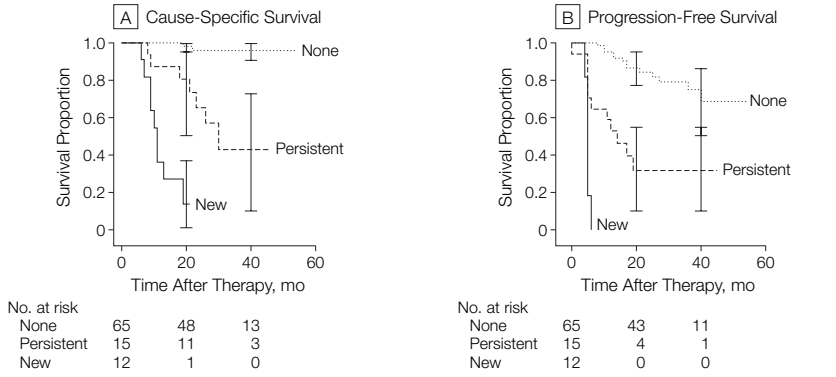
A prospective study was performed to validate the use of posttherapy FDG-PET as a predictor of clinical outcome in cervical carcinoma. Ninety-two patients with cervical cancer who were prospectively enrolled in a tumor registry at the time of diagnosis met the criteria for this study. In the validation patient data set (n = 92), posttherapy FDG-PET showed a complete metabolic response in 65 patients (70%). There was persistent abnormal FDG uptake in the irradiated region (cervix/lymph nodes) in 15 patients (16%). New anatomic sites of FDG uptake outside of the irradiated region were identified in 12 patients (13%). Cause-specific survival rates as a function of site of posttherapy FDG-PET results are shown in FIGURE 2A. The 3-year

Figure 1. Updated Cause-Specific and Progression-Free Survival Rates for Patients



Data to a mean follow-up of 28 months previously reported by Grigsby et al.[14] No sites of abnormal F-18 fluorodeoxyglucose (FDG) uptake on follow-up positron emission tomography defines the none group, persistent FDG uptake in the irradiated region defines the persistent group, and new sites of abnormal FDG uptake outside of the irradiated region defines the new group (log-rank $P<.001$ for both plots). Error bars indicate 95% confidence intervals.

Figure 2. Cause-Specific and Progression-Free Survival Rates for Patients



Data are from the prospective data set with no sites of abnormal F-18 fluorodeoxyglucose (FDG) uptake on follow-up positron emission tomography (none group), persistent FDG uptake in the irradiated region (persistent group), and new sites of abnormal FDG uptake outside of the irradiated region (new group) (log-rank $P<.001$ for both plots) Error bars indicate 95% confidence intervals.

cause-specific survival rates were 96% for those patients with a complete metabolic response on the posttherapy FDG-PET and 43% for those patients with persistent FDG uptake in the irradiated region. For patients with any new sites of FDG uptake on follow-up PET, the 2-year cause-specific survival rate was 14% ($P<.001$).

Figure 2B demonstrates the corresponding 3-year progression-free survival rates. The 3-year progression-free survival rates were 78% for those patients with a complete metabolic response on posttherapy FDG-PET, 33% for those patients with persistent FDG uptake in the irradiated region, and 0% for those with new sites of FDG uptake outside of the initial irradiated region ($P<.001$).

Cox proportional hazards modeling for disease recurrence showed that progressive disease demonstrated on the 3-month posttherapy FDG-PET was the most significant predictive factor of progression-free survival ($P<.001$) with a hazard ratio (HR) of 32.57 (95% confidence interval [CI], 10.22-103.82) (TABLE 2). The HR for a partial metabolic response on the 3-month posttherapy FDG-PET was 6.30 (95% CI, 2.73-14.56; $P<.001$). Pretreatment lymph node status remained a statistically significant predictor of progression-free survival in this model ($P=.003$) with a HR of 3.54 (95% CI, 1.54-8.09). Pretreatment clinical stage, overall radiation treatment time, and number of cycles of chemotherapy were excluded from this final model because they failed to meet the .05 entry level criterion once the FDG-PET variable was entered into the model.

Salvage Therapy Based on Posttherapy FDG-PET

When we began performing posttherapy FDG-PET in 1998, the significance of metabolically active areas on posttherapy PET was unknown. Initially, these lesions were followed up clinically using both physical examination and additional imaging studies. The timing of active interventions to address these lesions was individualized and was left to the discretion of the treating physician.

Once the prognostic significance of metabolically active lesions had been more clearly defined, active interventions based on the posttherapy PET findings were undertaken in a more systematic and timely fashion. No comparison of outcome based on observation or active intervention based on posttherapy PET can be made in our patient population. However, in our initial and prospective patient cohorts, long-term survival was achieved for 8 patients whose salvage therapy was initiated and directed by findings on their 3-month posttherapy PET (TABLE 3). Sites of persistence for these patients were local in 4 (2 cervix, 1 uterus, 1 pel-

vic lymph node) and distant in 4 (3 para-aortic lymph node, 1 abdominal wall). Three patients were treated with surgery, 4 with additional radiation and chemotherapy, and 1 patient with a combination of surgery, radiation, and chemotherapy. All patients were clinically free of disease as of December 31, 2006, with a mean follow-up of 50 months (range, 16-79 months) after the recurrence was diagnosed and treated.

COMMENT

The current treatment strategy for locally advanced cervical cancer (definitive radiation with concurrently administered cisplatin chemotherapy) achieves local control in approximately 70% to 80% of patients.[4] However, as is the case with malignant diseases in other sites, some tumors do not respond completely to standard therapy. Clinicians are then faced with the challenge of early identification of nonresponders to decrease treatment failures and avoid the toxicity of futile treatment.

The concept of using FDG-PET to assess tumor response to therapy is based on in vitro studies that associate decreases in tumor cell glucose uptake with decreases in the fraction of viable tumor cells.[20] Clinically, the association between decreased tumor glucose uptake and treatment response has been documented in several small series for tumors of the breast, head and neck, gastrointestinal tract, and lymphoma.[21-27] In the majority of these studies, FDG-PET was performed after 1 to 2 cycles of chemotherapy rather than after completion of the entire course of planned therapy. Most of these studies have linked initial response to chemotherapy, as measured by FDG-PET, to clinical outcome. However, few studies have specifically addressed the impact of FDG-PET response on patient management in the posttherapy setting.[28]

In the posttreatment setting, FDG-PET has been used to identify response to a complete course of therapy (chemotherapy or chemoradiotherapy) for lymphoma.[29-32] The goal for this is to identify patients for appropriate immediate salvage therapy (eg, more intensive chemotherapy or stem cell transplant). Notably, the international working group's response criteria in lymphoma have recently been modified to include routine use of posttherapy FDG-PET for assessing response in patients with these tumors.[33] In these guidelines, visual assessment alone of the FDG-PET images was sufficient to determine therapeutic response.[34]

In a more limited fashion, FDG-PET has been used to assess response to a complete course of therapy for malignant disease in other sites, including lung and head and neck cancer.[35-39] The hesitation to use FDG-PET to evaluate treatment response is based on the assumption that local inflammation due to radiation may result in false-positive PET scans. On the contrary, recent evidence has shown that postradiation normal tissue FDG uptake does not interfere with the prognostic information provided by the FDG response in the tumor itself. In fact, normal tissue FDG uptake has been positively correlated with tumor metabolic response and superior survival outcomes after radiation therapy for lung cancer.[40]

The rationale for using posttherapy FDG-PET in cervical cancer is 2-fold. First, the posttherapy FDG-PET provides information that may impact the approach to salvage therapy. Historically, reported outcomes from salvage therapy for cervical carcinoma were poor.[5] Locally recurrent cervical cancer was most often detected as the presence of gross tumor on pelvic examination. Total pelvic exenteration, while potentially curative, was associated with significant patient morbidity and limited long-term survival (16% in 1 study).[5] For patients with distant failures, the results were even more dismal. These patients were often undiagnosed until they developed symptoms related to disease recurrence. Not surprisingly, this re-

Table 2. Results of Final Multivariate Proportional Hazards Model for Survival Outcome

	Posttherapy PET		
	Progressive Disease	Persistent Disease	Lymph Node Status by Pretreatment PET
Coefficient	3.48	1.84	1.26
SE	0.59	0.43	0.42
Coefficient/SE	5.89	4.31	2.99
χ^2	34.69	18.56	8.92
Hazard ratio (95% CI)	32.57 (10.22-103.82)	6.30 (2.73-14.56)	3.54 (1.54-8.09)
P value	<.001	<.001	.003

Abbreviations: CI, confidence interval; PET, positron emission tomography; SE, standard error.

Table 3. Characteristics of Patients Undergoing Salvage Therapy[a]

Patient No.	Initial FIGO Stage	Pretreatment FDG-PET Lymph Node Status	Site of Recurrence on Posttherapy FDG-PET	Type of Recurrence Treatment	Disease-Free Period Since Recurrence, mo
1	Ib1	None	Pelvic lymph nodes	RT + chemotherapy	44
2	IIb	None	Para-aortic lymph nodes	Surgery + RT + chemotherapy	29
3	IIb	Pelvic	Cervix	Surgery	30
4	IIb	Pelvic	Para-aortic lymph nodes	RT + chemotherapy	78
5	Ib1	Pelvic	Abdominal wall	RT + chemotherapy	79
6	Ib2	Pelvic	Uterus	Surgery	53
7	Ib2	Pelvic	Para-aortic lymph nodes	RT + chemotherapy	47
8	IIa	None	Cervix	Surgery	16

Abbreviations: FDG-PET, positron emission tomography with F-18 fluorodeoxyglucose; FIGO, International Federation of Gynecology and Obstetrics; RT, radiation therapy.
[a] Includes patients from both cohorts.

sulted in poor rates of success for salvage therapy. In 1994, Grigsby et al[41] reported no survivors at 2 years for patients with isolated recurrences in the paraaortic lymph node chain.

Recent data have suggested that early detection of cervical cancer recurrence has the potential to significantly affect the outcome of salvage therapy. This is particularly true in the subset of patients with asymptomatic disease recurrences.[13] Hong et al[8] reported a 5-year survival rate of 22% for patients with recurrent tumors confined to the cervix vs 9% for recurrent tumors extending beyond the cervix and 4% involving adjacent tissues. In addition, the 5-year overall survival rate for patients treated with salvage surgery was 29% vs 3% for patients who did not qualify for surgery. Surgeries performed included total hysterectomy and radical hysterectomy in qualifying patients. For distant failures, we have reported a 100% 5-year survival rate for patients with isolated asymptomatic paraaortic lymph node recurrence treated with salvage concurrent chemoradiation.[9] The potential exists for durable salvage in patients with recurrent cervical cancer if early detection of these lesions can be achieved. Several small retrospective series have recently described modifications to posttherapy management based on PET.[42-44] We have now demonstrated in this study that active interventions sought as a result of posttherapy PET can result in long-term survival for a small group of patients. Additional follow-up with more patients is needed to confirm the impact of posttreatment PET on salvage therapy outcomes for patients with asymptomatic disease recurrences.

Tumor stage as defined by the International Federation of Gynecology and Obstetrics staging system has been a predictor of outcome in cervical cancer. We reported that lymph node stage (region of lymph node involvement identified by FDG-PET at the time of diagnosis) was more predictive of outcome than International Federation of Gynecology and Obstetrics stage, patient age, or tumor histology.[6] In the current study, we have found that progressive metastatic disease and an incomplete metabolic response by posttherapy FDG-PET are more predictive of clinical outcome than the pretreatment tumor characteristics including clinical stage and pretreatment lymph node status and the treatment-related variables, overall radiation treatment time, and number of cycles of chemotherapy.

The second and most important rationale for using posttherapy FDG-PET in cervical cancer is to provide valuable long-term prognostic information only 3 months after the completion of therapy. We propose that this information may be used to select patients for additional therapy on clinical trials. We have now prospectively validated the use of posttherapy FDG-PET as a metabolic biomarker of tumor response in cervical cancer. Complete metabolic response is associated with excellent survival outcome (3-year cause-specific survival rate of 96%). These patients require no immediate additional therapy. Partial metabolic response is associated with intermediate survival outcome (3-year cause-specific survival rate of 43%) and decreased progression-free survival (3-year progression-free survival rate of 33%). We propose that patients with partial metabolic response on follow-up FDG-PET should be considered for additional therapeutic clinical trials. New sites of metabolic activity on posttherapy FDG-PET are associated with very poor survival outcome (2-year cause-specific survival rate of 14%). These patients have developed metastatic disease within 3 months of completing therapy and should be enrolled in clinical trials designed to explore novel treatment strategies for refractory cervical cancer. Clinical trials to test the utility of the early detection and treatment of incomplete metabolic responders and those with new sites of metastatic disease are being developed at our institution.

The primary limitation of this study is that it is a single institution study of 92 patients. Our findings may not be generalized across all centers. Image acquisition and interpretation procedures are standardized at our institution. The quality of the acquired FDG-PET/CT image can vary based on several factors such as the dose of FDG injected, patient fasting before FDG injection, blood glucose level at the time of injection, and time from injection to image acquisition. Technical issues such as image acquisition protocols will need to be standardized. Interpretation of PET scans by visual assessment appears to be adequate for determining whether PET is positive or negative.[34] However, image interpretation is dependant on the experience of the imaging physicians and input from the treating physicians. Our findings should be replicated in larger multisite studies using other study populations.

In summary, in this single institution prospective study, the 3-month posttherapy FDG-PET provided an immediate measure of response to therapy and was a robust predictor of outcome to treatment for cervical cancer. This finding should be replicated in a larger multiinstitutional setting. If this finding is verified by others, we recommend designing clinical trials to explore novel therapies for patients with either partial metabolic response or progressive disease on posttherapy FDG-PET.

Author Contributions: Dr Grigsby had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Schwarz, Siegel, Grigsby.
Acquisition of data: Dehdashti, Grigsby.
Analysis and interpretation of data: Schwarz, Siegel, Grigsby.
Drafting of the manuscript: Schwarz, Siegel.
Critical revision of the manuscript for important intellectual content: Schwarz, Siegel, Dehdashti, Grigsby.
Statistical analysis: Schwarz, Grigsby.
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