Influence of Diabetes on the Interpretation of PET Scans in Patients With Esophageal Cancer

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ABSTRACT

Purpose: Patients with diabetes mellitus (DM) can have altered sugar transport into cells, potentially affecting the results of 18-FDG PET scans. The specific aim of this study was to determine the effect of DM on pre- and posttreatment standard uptake value (SUV) scores in patients undergoing chemoradiotherapy for esophageal cancer.

Methods: Patients with locally advanced esophageal carcinoma undergoing preoperative or definitive chemoradiotherapy underwent pre- and posttreatment 18-FDG PET scans. Maximum SUV score was measured from the tumor before chemoradiotherapy and 3 to 4 weeks after chemoradiotherapy (preoperatively). Patients were identified as having DM by medical record review. Random serum glucose measurements were obtained prior to 18-FDG PET scans. The Wilcoxon signed-rank test was used to test for differences in SUV scores between patients with and without DM, and a generalized linear model with backward selection was applied to search for significant predictors of initial and posttreatment SUV scores.

Results: Sixty-three patients underwent 18-FDG PET scans during the course of treatment for esophageal malignancies between 6/02 and 8/05. Fifty-four patients received chemotherapy. The median radiation dose was 46.8 Gy. Eighteen patients had DM, six were insulin-dependent DM (IDDM). There was no difference in initial SUV scores between DM and non-DM patients ($P > .05$). There was also no difference in initial SUV scores between IDDM and non-IDDM groups. Patients with tumors at the gastroesophageal junction had lower initial SUV scores compared to patients with tumors in the lower or mid-esophagus ($P = .05$). T stage was associated with initial SUV score (T2 lower than T3, $P = .014$). Older age ($P = .03$), diabetes ($P = .007$), higher T stage ($P = .002$), and presence of nodes ($P = .05$) were each positively associated with posttreatment SUV scores. Blood glucose levels prior to 18-FDG PET scan, endoscopic tumor length, and tumor location were not predictive of posttreatment SUV scores. Patients with DM had significantly lower posttreatment SUV scores compared to patients without DM ($P = .04$). Pathologic complete response or percent SUV decrease did not differ between patients with or without DM.

Conclusion: Regardless of glucose levels, DM and IDDM do not influence pretreatment SUV scores in patients with localized esophageal cancer. However, DM may influence posttreatment SUV scores and thus complicate interpretation of treatment response. Further confirmatory study in a larger cohort of DM patients to evaluate the relationship of posttreatment SUV score to pathologic response is warranted.

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Standard guidelines suggest use of computed tomography (CT) or magnetic resonance imaging (MRI) when planning radiotherapy treatment for esophageal cancer; however, positron emission tomography (PET) with infusion of the glucose analog [F-18]-2-deoxy-2-fluoro-D-glucose (^{18}F-FDG) has also been accepted for staging as well as to guide radiotherapy treatment planning for these patients. A

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recent review found PET scans to have poor sensitivity (51%) and specificity (81%) in determining local and regional metastasis in patients with esophageal cancer, but acceptable sensitivity (67%) and specificity (97%) for distant metastasis.[1] PET scans can also aid in the planning and design of radiation treatment fields in patients with esophageal cancers treated with radiation.[2–4]

PET scanning relies on a molecular shift in glucose transporters in cancer cells that results in increased uptake of glucose within these cells. This molecular shift is reflected in an increase in GLUT-1 transport proteins, as well as increased levels or activity of hexokinase, which leads to increased uptake and retention of glucose analog ^{18}F-FDG in cancer cells compared to normal cells as reflected by standard uptake value (SUV) scores, which are higher in neoplasms than normal tissues.[5]

The pathophysiology of diabetes mellitus (DM) has been well documented. Patients with type 1 DM have an insulin deficiency that decreases normal glucose uptake in cells, primarily through GLUT-4 transporters. This decrease in blood glucose uptake results in a rise in blood glucose. Patients with type 2 DM have inadequate insulin receptors leading to an inability of insulin to bind to receptors causing an increase in blood glucose. Several studies have reported that increased blood glucose levels lead to decreased tumor uptake of ^{18}F-FDG.[6–11] However, results of ^{18}F-FDG uptake in various malignancies in patients with DM alone, but normal glucose levels, have been mixed.[6,7,12–14] In addition, there have been mixed results of patients with type 1 DM having decreased tumor uptake of ^{18}F-FDG as compared to patients with type 2 DM.[12,14,15] It is suggested that this decreased uptake of ^{18}F-FDG in patients with type 1 DM may be due to insulin supplementation "stealing" ^{18}F-FDG into normal cells, thus decreasing the available amount of ^{18}F-FDG for cancer cells.

None of the previously cited studies evaluated the effect of DM on PET scans in patients with esophageal cancer. Therefore, we investigated the effect of DM in interpreting both pre- and postchemoradiotherapy PET scans in patients with esophageal cancers, as this may influence interpretation of response to chemoradiotherapy and future treatment decisions.

PATIENTS AND METHODS

Beginning in June 2002, patients diagnosed with adenocarcinoma or squamous cell carcinoma of the esophagus underwent PET/CT, in addition to standard staging studies, including endoscopic ultrasound (EUS) and diagnostic CT, prior to undergoing combined-modality chemotherapy and radiotherapy at Fox Chase Cancer Center. The PET/CT scans were usually obtained prior to the initiation of any cytotoxic therapy and were repeated 4 to 6 weeks after completion of treatment, prior to planned esophagectomy in patients undergoing preoperative chemoradiotherapy. Our PET/CT procedures have been published previously.[2] A maximum SUV score was obtained from the tumor.

All patients underwent CT simulation with the PET scan images fused with the CT simulation images to determine the gross tumor volume (GTV) and planning tumor volume (PTV). Patients were initially treated with anterior/posterior (AP) and posterior/anterior (PA) fields with 6- or 10-MV photon beams. An AP and two posterior oblique fields were incorporated into treatment to limit spinal cord exposure to no more than 45 Gy. Customized blocks were used to protect normal tissue. The usual field borders were 5 cm superior, 3 cm inferior, and 2.5–3 cm lateral to the GTV, as outlined by CT and PET scans. Chemotherapy regimen was at the discretion of the treating medical oncologist.

The clinical data were obtained from retrospective chart reviews. Survival analysis was performed from the date of diagnosis. Patients who died of non-cancer–related causes after completion of therapy without evidence of cancer were censored at the time of death. Patients with locally advanced disease receiving palliative radiotherapy who died during treatment were coded as having local persistence of disease. The Wilcoxon signed-rank test was used to determine association of selected variables to initial tumor SUV.[16] A generalized linear model was used with backward selection to find significant independent predictors for initial and post-treatment SUV.[17] The study was reviewed and approved by the Fox Chase Cancer Center Institutional Review Board.

Table 1. Patient characteristics

Characteristic	Number
Sex	
Male	54
Female	9
Median age in years (range)	67 (37–97)
Diabetes mellitus	
No	45
Yes	18
Location	
Cervical esophagus	1
Middle	11
Lower	23
Gastroesophageal junction	28
T stage	
T2	5
T3	42
T4	2
Overall stage	
IIA	5
IIB	3
III	29
IVA	11
IVB	1
Resection	
R0	25
R1	3
R2	1
Chemotherapy	
Cisplatin + 5-fluorouracil	36
Paclitaxel, cisplatin + 5-fluorouracil	11
5-fluorouracil	3
5-fluorouracil + paclitaxel	1
Paclitaxel	1
Capecitabine	1

RESULTS

Sixty-three patients underwent ^{18}F-FDG PET scans during their course of treatment for esophageal malignancies between 6/02 and 8/05. The patient characteristics upon which this report is based are listed in Table 1. Forty-two patients underwent both pre- and postchemoradiotherapy PET scans. The pathologic response rate is based upon complete pathologic examination of the 29 patients undergoing Ivor-Lewis esophagectomy. The median radiation dose administered was 46.8 Gy (range, 7.2–62.1). Twelve patients had non–insulin-dependent diabetes mellitus (NIDDM), and 6 had insulin-dependent diabetes mellitus (IDDM). There was no statistical difference ($P > .05$) in blood glucose levels at the time of the pretreatment PET scans between patients with and without DM. Likewise, there was no difference in blood glucose prior to the post-

Table 2. Mean pre- and posttreatment SUV and percent SUV decrease by diabetes mellitus status

	No diabetes mellitus Mean (range; ± SD)	Diabetes mellitus Mean (range; ± SD)	*P* value
Pre-treatment SUV	8.7 (1.6–2; ± 5.6)	10.1 (0–23; ± 5.9)	.44
Post-treatment SUV	3.7 (1.4–6.2; ± 1.24)	2.8 (0–5.5; ±1.29)	.04
Percent SUV decrease	-53% (+12.5% – -80%; ± 22.5%)	-58% (0% – -84%; ± 22.5%)	.49

Abbreviations: SUV = standard uptake value; SD = standard deviation

treatment PET scans when comparing diabetic and nondiabetic patients.

Table 2 shows the pre- and posttreatment SUV scores as well as percent SUV decrease by DM status. No difference was noted between patients with IDDM and NIDDM in any of the studied variables. Patient numbers, however, are small in each group, limiting the power to detect small differences between groups.

Tumors at the middle, lower, and gastroesophageal junction (GEJ) had mean pretreatment SUV scores of 11.6, 11.0, and 7.7, respectively. Tumors at the GEJ had statistically significant lower scores compared with those at the middle and lower esophagus ($P = .05$). Posttreatment SUV scores comparing GEJ tumors to middle or lower esophageal tumors were not statistically different ($P = .17$).

Nine patients had N1 disease at posttreatment evaluation who did not have PET-positive nodes prior to treatment. Three of these patients had diabetes. The diabetic patients had higher mean scores in initial SUV, posttreatment SUV, and SUV decrease compared to nondiabetic patients. The difference in posttreatment SUV was statistically significant ($P = .05$).

Variables examined as predictors for SUV scores were age, sex, diabetes, insulin use, T and N classification, endoscopic tumor length, glucose levels, and tumor location. With backward selection, only T2 classified tumors predicted for a lower pretreatment SUV, as compared with T3/T4 tumors (P=.014). Examining post-treatment SUV score predictors, diabetes ($P = .007$), T2 cancers ($P = .002$), and positive lymph nodes ($P = .0484$) all had lower SUV scores. Age was also predictive, with older patients having lower posttreatment SUV scores ($P = .048$).

DISCUSSION

^{18}F-FDG PET scans are currently used in esophageal cancer for the purposes of staging, treatment planning, and assessment of response to treatment. The mechanism of uptake of ^{18}F-FDG is based on the physiology of the tumor cell. A molecular shift within the cell leads to increased GLUT-1 transport proteins, as well as an increased level or activity of hexokinase.[5] GLUT-1 transports glucose across the cell membrane, down a gradient, with minimal activation from insulin. Hexokinase then traps the glucose inside the cell. Increased metabolic needs of the tumor lead to these shifts, in which glucose is taken up more than in the normal cells surrounding it. ^{18}F-FDG is a glucose analog competing with glucose for the GLUT-1 receptor and other glucose transport proteins. Increased competition for the glucose transporter with ^{18}F-FDG glucose would be expected in a patient with an increased blood glucose level. Several studies have shown that an increased blood glucose level decreases SUV in a variety of tumors.[6–10,15]

In 1994, Bares et al published their results of a prospective study that evaluated the diagnostic performance of ^{18}F-FDG PET compared to CT and ultrasound in 40 patients with pancreatic cancer.[14] The investigators reported a decrease in SUV scores in patients with DM, independent of glucose levels. All patients fasted for 12 hours prior to the PET scan, and serum glucose was measured immediately before, 20, and 40 minutes after the PET scan. Although not the primary objective, Bares recognized that decreased SUV scores only occurred in patients with DM. Furthermore, patients with IDDM had decreased tumor uptake, regardless of blood glucose levels, accounting for most of the false-negative PET scan findings. Both of these results would suggest that decreased tumor uptake in diabetic patients is not a function of serum glucose levels, but rather of glucose transport at the level of cancer cells. Results of this study, however, stand in contrast to a 2004 report by Gorenberg et al.[12]

Gorenberg retrospectively examined ^{18}F-FDG uptake in lung tumors in patients with and without DM. All patients fasted for 6 hours prior to PET scan; IDDM patients were encouraged to take their normal insulin dose. Blood glucose between the two groups was not statistically significant; however, blood glucose levels above normal (> 7.0 mmol/L) were allowed in the DM group, but not in the non-DM group. No significant difference in SUV levels was found, though the small number of patients did not allow comparison of patients with IDDM to NIDDM patients. Further, as blood glucose increased over 7.0 mmol/L, patients with DM did not have significant increases in SUV scores. This could represent a deficiency in ^{18}F-FDG uptake with an unknown threshold.

Our study investigated the influence of diabetes independent of blood glucose levels on both pre- and posttreatment esophageal cancers. This is the first study examining the relationship between DM and SUV uptake in patients with esophageal cancer. We found no significant differences in SUV scores prior to treatment between diabetic and nondiabetic patients ($P = .44$). These results are consistent with that of Gorenberg et al.[12] This was expected, as with no increase in glucose competing with ^{18}F-FDG, one would anticipate SUV score levels to be similar between those with or without diabetes. Further, insulin-dependent diabetics and non–insulin-dependent diabetics did not differ in SUV scores. This is a somewhat more surprising result, as one might expect a patient who is supplementing insulin to have a decreased SUV score in tumors, due to the mechanism of insulin "stealing" glucose and ^{18}F-FDG into normal cells and away from tumor cells. However, data about individual insulin levels prior to treatment were not available for anlysis. Because patients are instructed to fast before PET scanning, they are also often instructed to refrain from using insulin during this fast as it may lead to hypoglycemia. Our patients were not hypoglycemic, but still may have refrained from supplementing insulin before their PET scan.

Using backwards selection, only T2

classification presented itself as a predictor of lower SUV scores, as compared to T3/T4 class tumors ($P = .014$). This result is not unexpected, as T2 tumors tend to be smaller and hence the potential for fewer tumor cells to accumulate ^{18}F-FDG.

After chemoradiotherapy, PET scanning was repeated to determine response to therapy. Curiously, after chemoradiotherapy, SUV scores were significantly lower in diabetics vs. nondiabetics ($P = .04$). Further predictors of post-treatment SUV scores included T2 cancers ($P = .002$) and positive lymph nodes ($P = .0484$), all of which were associated with lower SUV scores. Age also predicted a lower posttreatment SUV score, with older patients having lower scores ($P = .048$). Insulin supplementation, again, did not demonstrate any statistical difference vs. that of non–insulin-dependent diabetics, but patient numbers in this study were relatively small. These results would suggest that patients with DM, as well as those with positive lymph nodes and of older age, may respond better to treatment; however, the percent decrease in SUV was not significantly different between these groups, thus eliminating the possibility that these patients responded to treatment better.

These conflicting results may be attributable to study limitations, with the major limitation in this case being small sample size. Thus, our results must be viewed as hypotheses-generating and should be followed with a larger population. In addition, as mentioned above, insulin levels for individual patients were not available, which could explain the nonsignificant results in both pre- and posttreatment patients with IDDM. A high level of insulin would suggest that insulin does not play a role in ^{18}F-FDG uptake. A normal or low level of insulin would explain the observed results, assuming that insulin does "steal" glucose from tumor cells as previously suggested.[12,14,15]

These results are clinically applicable in several areas, the first of which is staging. Although ^{18}F-FDG PET scanning for staging is limited to that of distant metastasis, it is possible that these results could be extrapolated to suggest that diabetes would not influence PET staging of distant metastasis. Further, it would appear that diabetes would not influence GTV delineation of PET/CT fusion for the purposes of accurate radiation treatment planning.

Finally, and perhaps most importantly, diabetes may influence the interpretation of a complete or pathologic response in postchemoradiotherapy patients. Recently, Song et al investigated the ability of ^{18}F-FDG PET to predict a pathologic response in posttreatment esophageal cancer patients.[18] They reported that pathologic response strongly correlated with metabolic response in highly metabolic tumors, with an SUV > 4.0. The Radiation Therapy Oncology Group 0246 trial is examining the feasibility of a nonsurgical approach, using induction chemotherapy followed by chemoradiotherapy. Eligibility for salvage surgery is determined with CT and EUS — both of which are mandatory — and PET, which is encouraged. Should diabetes confound posttreatment SUV scores, it is possible that DM could lead to misinterpretation of a metabolic response, leading to misinterpretation of a pathologic response and a delay or denial of necessary surgery.

In conclusion, DM, younger age, T classification, and positive lymph nodes all appear to influence postchemoradiotherapy treatment SUV scores. Further, our data suggest DM, independent of glucose levels, does not influence prechemoradiotherapy treatment SUV scores, though T classification might. To determine the validity of our results, further confirmatory studies are warranted in a larger cohort of patients with DM to evaluate the relationship of posttreatment SUV to pathologic response.

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Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.