Positron Emission Tomography for Response Assessment in Desmoplastic Small Round Cell Tumor

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Background: Desmoplastic small round cell tumors (DSRCT) typically have a large stromal component and often are extensively disseminated in the peritoneal cavity at diagnosis. These factors contribute to difficulty in quantifying response to chemotherapy using RECIST or WHO criteria. This study compares the overall disease response to chemotherapy by fluorodeoxyglucose-positron emission tomography (FDG-PET) and computed tomography (CT) in patients with DSRCT.

Methods: We conducted a retrospective chart review of 7 patients with DSRCT who were imaged by FDG-PET and CT at diagnosis and after 3 cycles of chemotherapy. Response to chemotherapy was graded according to EORTC metabolic response guidelines and RECIST.

Results: All tumors demonstrated some decrease in SUVmax (51% ± 21%) and longest diameter (23% ± 8%) with chemotherapy. The best response achieved by FDG-PET was a partial response in 6 patients and by CT was a partial response in 1 patient. Measured response was concordant between the 2 modalities in 2 patients.

Conclusions: In this small series response measurement by FDG-PET did not always correlate with response measurement by CT. A greater decrease in metabolic activity as compared with size was seen in all patients. Further studies are needed to define the role of FDG-PET in assessing early response of DSRCT to chemotherapy.

Key Words: desmoplastic small round cell tumor, positron emission tomography, response assessment

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Desmoplastic small round cell tumor (DSRCT) is a rare, aggressive tumor of adolescence characterized by the chromosomal translocation t(11;22)(p13;q12) that generates a novel, chimeric transcription factor EWS-WT1. At diagnosis, the majority of patients have an abdominal-pelvic mass with widespread intra-abdominal serosal involvement that is not related to a particular organ system. Primary sites of DSRCT have also been reported in the thoracic cavity, testicle, sinuses, and bone.1,2 There is often widely disseminated disease at diagnosis.

There is no currently accepted standard of care for newly diagnosed patients with DSRCT, though for the majority of patients therapy currently includes high-dose alkylator-based chemotherapy, aggressive surgical debulk- ing with a goal of >90% resection, and radiotherapy. Response to chemotherapy has historically been difficult to quantify by Response Evaluation Criteria in Solid Tumors (RECIST) or WHO criteria given these tumors’ large stromal component and often extensive dissemination in the peritoneal cavity at diagnosis. [18F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional imaging modality that quantifies tissue metabolic activity using the glucose analog FDG tagged with a positron-emitting isotope fluorine-18. A potential use of FDG-PET in the assessment of response to chemotherapy in other pediatric sarcomas has been demonstrated.3 FDG-PET imaging is currently used to follow response to treatment in some patients with DSRCT, but limited data has been reported on the utility of FDG-PET in this disease.

We report here the experience of FDG-PET imaging to assess disease response in newly diagnosed patients with DSRCT at our center.

PATIENTS AND METHODS

Patient Population

A retrospective chart review was conducted to identify patients diagnosed with DSRCT who were imaged by both FDG-PET and computed tomography (CT) at diagnosis and after 3 cycles of chemotherapy between January 2004 and December 2009 in the Department of Pediatrics at MSKCC. Age, sex, site, and dissemination of disease, treatment regimen used, and results of imaging studies were reviewed for all patients. The institutional review board at MSKCC approved the review of medical records for this analysis.

FDG-PET Imaging and Scan Review

Patients were imaged after at least 6 hours of fasting. Fingerstick blood sugar was obtained and patients were injected when blood sugar levels were <200 mg/dL. After intravenous injection of 407 to 629 MBq of [18F]-FDG and an uptake period of 57 to 80 minutes patients were imaged on the General Electric Advance PET, Discovery LS PET/CT (General Electric Medical Systems, Milwaukee, WI) or the Biograph PET/CT scanner (CTI; Siemens Medical Systems, Malvern, PA). After iterative reconstruction and attenuation correction, images were displayed in axial, coronal, and sagittal planes for analysis. All patients were also imaged by conventional CT of the chest, abdomen, and pelvis with IV and oral contrast. One of the FDG-PET scans and 4 of the CT scans were performed outside our institution.
FDG-PET studies were retrospectively reviewed by a nuclear medicine physician, and CT studies were retrospectively reviewed by 2 pediatric radiologists. Target lesions were identified. Data collected included tumor maximum standard uptake value (SUV max) of each study, the SUV max of each of each patient’s target lesions, and the sum of the longest diameters of target lesions. The SUV max of all lesions in each patient were combined, and a mean SUV max was also calculated for each patient. Response to chemotherapy was graded according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) PET study group 4 and RECIST 5.

RESULTS
Seven patients were identified. All had molecularly confirmed, biopsy-proven DSRCT. There were 6 males and 1 female. The median age at diagnosis was 18.6 years (range, 15 to 24.6y). Initial staging evaluation included FDG-PET and conventional CT in all patients before the receipt of chemotherapy. No tumors were located outside of the abdomen and pelvis. A minimum of 1 and a maximum of 4 lesions were identified per patient. There was a mean of 3.9 ± 2.7 days between the pretreatment FDG-PET and CT. All patients received 3 cycles of chemotherapy consisting of cyclophosphamide (2.1 mg/m²/d) for 2 days, doxorubicin (37.5 mg/m²/d) for 2 days, and vincristine (2 mg/m²). All patients were reimaged after cycle 3 with both FDG-PET and conventional CT. There was a mean of 0.7 ± 0.8 days between performance of the second FDG-PET and CT. One patient had a debulking operation performed before initial staging evaluation, but measurable disease remained after the surgery. Six of the 7 patients proceeded to surgery after the second FDG-PET and CT, and all patients continued with planned chemotherapy after recovery from either surgery (6 patients) or cycle 3 of chemotherapy (1 patient).

The tumor SUV max ranged from 6.9 to 25 (mean, 12) at diagnosis and from 3 to 11 (mean, 5) after 3 cycles of chemotherapy. Tumor size ranged from 4.1 to 22.6 cm (mean, 14.5 cm) at diagnosis and from 3.3 to 17.5 cm (mean, 11 cm) after 3 cycles of chemotherapy (Table 1). Using the EORTC metabolic response guidelines, metabolic complete response (resolution of FDG uptake within tumor) was observed in 3 lesions, metabolic partial response (PR) (>25% reduction in tumor SUV uptake) in 13 lesions, and metabolic stable disease (SD) (change in tumor SUV of <25%) in 1 lesion. Overall, no patients experienced a metabolic complete response, 6 achieved a metabolic PR, and 1 metabolic SD (Table 2). By RECIST, 1 patient experienced a PR and the remaining 6 patients had SD. All tumors demonstrated some decrease in SUV max (51% ± 21%) and longest diameter (23% ± 8%) with chemotherapy. The best response achieved by FDG-PET was a PR in 6 patients and by CT was a PR in 1 patient. Measured response was concordant between the 2 modalities in 2 patients.

DISCUSSION
The current practice for assessing pediatric sarcomas’ response to therapy is by size measurement on CT or magnetic resonance imaging. The utility of FDG-PET imaging in the management of pediatric sarcomas has been reported as an adjunct in staging 6,7 for evaluating response to chemotherapy in bone sarcomas, 3 for predicting outcome for Ewing sarcoma, 8 and as an adjunct to detecting recurrent disease. 9 The practice at our institution is to follow response to treatment in patients with DSRCT using FDG-PET in addition to conventional imaging. The current series gives a descriptive account of FDG-PET used in conjunction with conventional imaging to assess response to chemotherapy after 3 cycles of chemotherapy before planned surgical resection.

A greater decrease in metabolic activity as compared with size was observed in all patients (Fig. 1). It has been demonstrated that RECIST underestimates tumor response to therapy in certain sarcomas 10,11 and that FDG-PET may better predict histologic response to chemotherapy than does size change. 12, 13 This is of particular interest for pediatric tumors in which histologic response to therapy has been shown to correlate with survival such as in osteosarcoma 14-16 and Ewing sarcoma. 17,18 In addition, FDG-PET response has been found to be associated with progression-free survival in osteosarcoma. 19 The predictive value of histologic response to treatment in DSRC has not been evaluated and a correlation between imaging and necrosis cannot be equated with a correlation between imaging and outcome; however, as FDG-PET becomes more routinely used to assess response to treatment in pediatric tumors, critical evaluation of both degree of necrosis with and early metabolic response to treatment as prognostic factors could be pursued.

In this series, measured response was concordant between FDG-PET and CT in only 2 patients. We suspect that the superior responses demonstrated by FDG-PET are a more accurate reflection of patients’ response to initial chemotherapy than are the disappointing responses seen on CT.

### Table 1. Tumor SUV max and Size Before and After Chemotherapy

<table>
<thead>
<tr>
<th></th>
<th>FDG-PET SUV max</th>
<th>Sum of Longest Diameter (cm) by CT</th>
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<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>Mean</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>6.9-25</td>
<td>3-11</td>
</tr>
</tbody>
</table>

CT indicates computed tomography; FDG-PET, fluorodeoxyglucose-positron emission tomography; SUV max, maximum standard uptake value.

### Table 2. FDG-PET Metabolic Response Assessment Results by EORTC Guidelines

<table>
<thead>
<tr>
<th>Metabolic Response</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Lesions</td>
<td>Patients</td>
</tr>
<tr>
<td>CR</td>
<td>3/17 (18%)</td>
</tr>
<tr>
<td>PR</td>
<td>13/17 (76%)</td>
</tr>
<tr>
<td>SD</td>
<td>1/17 (6%)</td>
</tr>
</tbody>
</table>

CR indicates complete response; EORTC, European Organization for Research and Treatment of Cancer; FDG-PET, fluorodeoxyglucose-positron emission tomography; PR, partial response; SD, stable disease.
CT. Because these tumors have a large stromal component, changes in size with chemotherapy are often minimal despite the majority of patients experiencing rapid symptomatic relief with administration of chemotherapy. FDG-PET may offer information different from CT in these patients, and that information could prove to be complementary. The adequacy of surgical resection is a determinant of patient outcome. Lack of measurable disease response to chemotherapy often keeps oncologists from recommending surgical resection. However, if a metabolic disease response can be demonstrated by FDG-PET, the surgeon and oncologist might be more willing to proceed to surgical resection. FDG-PET may also prove useful in disease surveillance off therapy as demonstrated by Kushner et al in the case of a patient found to have a solitary recurrence in the soft tissue of the leg, which would not have been detected by standard imaging directed at the chest, abdomen, and pelvis. Zhang et al also reported a case of DSRCT with metastatic disease to the right ilium; this site of disease was detected by FDG-PET but not by CT.

The results of conventional treatment for DSRCT remain disappointing. The unique chimeric transcription factor EWS-WT1 raises hope that a targeted agent will be identified. Changes in size have been inadequate in assessing response to targeted therapies in several solid tumors. The adequacy of surgical resection is a determinant of patient outcome. Lack of measurable disease response to chemotherapy often keeps oncologists from recommending surgical resection. However, if a metabolic disease response can be demonstrated by FDG-PET, the surgeon and oncologist might be more willing to proceed to surgical resection. FDG-PET may also prove useful in disease surveillance off therapy as demonstrated by Kushner et al in the case of a patient found to have a solitary recurrence in the soft tissue of the leg, which would not have been detected by standard imaging directed at the chest, abdomen, and pelvis. Zhang et al also reported a case of DSRCT with metastatic disease to the right ilium; this site of disease was detected by FDG-PET but not by CT.

The current review is limited in that it is a retrospective examination of a small series of patients at a single institution. The intent of this study is descriptive given the limited number of patients and no definitive conclusions can be drawn. It is impossible to know whether greater size decreases would have eventually followed the early responses seen by FDG-PET, as 6 of the 7 patients proceeded to surgical resection of disease after their post-cycle 3 radiographic assessments. Prospective studies of patients with DSRCT are difficult given the rarity of the disease though the use of FDG-PET in patients with DSRCT is being further explored as a secondary objective in a pilot trial of irinotecan, temozolomide, and bevacizumab in patients with newly diagnosed DSRCT.

REFERENCES


FIGURE 1. A 15-year-old boy with a primary pelvic DSRCT. A, Pretreatment FDG-PET scan shows a hypermetabolic mass with an SUV of 25. The longest diameter by CT was 15.2 cm. B, After 3 cycles of chemotherapy, the SUV has decreased by 80% to 5. The longest diameter decreased by 21%. DSRCT indicates desmoplastic small round cell tumors; FDG-PET, fluorodeoxyglucose-positron emission tomography; SUV, standard uptake value.