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## Incorporation of PET scanning into contemporary management programs for Hodgkin's disease

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In just the past decade, positron emission tomography with fluorine-18 fluorodeoxyglucose (PET scanning) has come to be considered an essential component of initial staging of Hodgkin's disease (HD) at many medical centers around the world. In addition, it is common to utilize PET scanning to evaluate response to treatment and to employ it as a component of routine surveillance programs.

### **Diagnostic PET imaging** *Initial Staging with PET*

A number of studies have compared the value of PET scanning with single photon emission tomographic gallium-67 scintigraphy (SPECT-gallium scanning) and computed tomographic scanning (CT) in the initial staging evaluation of patients with HD. Kostakoglu *et al.*<sup>1</sup> demonstrated 126 sites of disease in 44 patients with PET imaging whereas gallium scans were positive in only 81 sites. Bangerter *et al.*<sup>2</sup> compared the results of PET scanning on 44 patients who underwent conventional staging that included CT, ultrasound, radionuclide bone scans, bone marrow biopsy, liver biopsy and laparotomy. PET scans were positive in 38 of 44 patients at the sites of disease that were identified by conventional staging studies. PET scanning identified additional disease in five patients and affected the stage designation in 6 patients (14%). In all 6, a change in treatment strategy resulted.

Heultenschmidt *et al.*<sup>3</sup> performed a lesion by lesion comparison of PET scanning and convention imaging in 25 patients with HD. The change in stage designation was notable in this series: PET scanning led to a lower stage designation in 28% and a higher stage classification in 12% of patients.

Naumann *et al.*<sup>4</sup> looked specifically at patients with early stage Hodgkin's disease. PET scanning indicated a different clinical stage for 18 (20%) and in 16 of these 18 the management would have been changed. In another large series, Munker *et al.*<sup>5</sup> reported that 21 of 73 patients (29%) were upstaged by PET and only two patients

were downstaged.

Doberst *et al.*<sup>6</sup> evaluated 44 patients with Hodgkin's disease and correlated the results with histologic subtypes. They concluded that the histologic subtype did not influence the intensity of glucose metabolism or the likelihood of identifying disease by PET imaging.

These data and other similar series indicate an important role for initial PET scanning to define the precise extent of disease in patients with Hodgkin's disease. This may be especially important for patients who have otherwise early stage disease who would be candidates for current protocols employing only brief duration chemotherapy and low-dose involved-field radiation.

### *PET imaging at the completion of chemotherapy*

PET imaging at the completion of chemotherapy has been shown to correlate with ultimate outcome.<sup>7,8</sup> De Wit *et al.*<sup>7</sup> looked at the predicative value of CT scanning, erythrocyte sedimentation rate (ESR) and PET scanning. Only the post treatment PET scan correlated significantly with disease-free survival in the 50 patients who were studied. Guay *et al.*<sup>8</sup> reported a median disease-free interval of only 79 days for patients who had positive PET scans at the completion of chemotherapy.

Clinically, the most important management issue relates to patients who have residual mediastinal adenopathy based on anatomic imaging such as a CT scan or chest X-ray. PET scanning has been shown to be useful in differentiating patients who have residual disease from those who likely have only residual scarring and slowly regressing masses. Naumann *et al.*<sup>9</sup> studied 58 patients with residual abnormality on CT. 8 patients had positive PET scans and 5 of these relapsed whereas only 2 of 50 patients with negative PET scans relapsed.

Weihsrauch evaluated 28 patients who had residual mediastinal abnormality. 16 of 19 patients with negative PET imaging remained in remission. However, regression

or relapse occurred in 60% of patients who had a positive PET scan. Panizo *et al.*<sup>10</sup> performed PET scans on 29 patients who had residual mediastinal masses. None of the 17 patients with negative scans relapsed but 9 of 12 patients with positive scans relapsed or progressed within 1 year.

An important question is whether alteration of treatment based on the results of the post-treatment PET scans may favorably affect outcome. De Wit *et al.*<sup>11</sup> evaluated outcome in 17 patients who had positive PET scans in conjunction with residual masses after completion of chemotherapy. Four patients received radiation therapy after the PET scan and with a median followup just beyond 1 year none had relapsed. The majority of patients who received no further therapy relapsed. Advani *et al.*<sup>12</sup> looked at 81 patients treated with Stanford V chemotherapy who had pre-treatment and post-treatment PET scans. Six of 81 patients (7%) had positive PET scans at the completion of chemotherapy. Three of these presented initially with bulky mediastinal involvement. All patients had radiation therapy that included sites positive on PET imaging. Two of the 3 patients subsequently progressed despite consolidative irradiation.

The key question with respect to post-chemotherapy PET scanning in patients with Hodgkin's disease is whether a planned alteration in treatment based on the results of PET scan will be associated with an improved outcome.

#### *PET scanning as an early treatment response indicator*

Hoekstra *et al.*<sup>13</sup> were among the first to suggest that PET scanning could be used as an early treatment response indicator for lymphoma. They showed that patients who ultimately achieved a complete response had negative PET scans after only 2 courses of chemotherapy. Furthermore, metabolic tumor activity decreased after only a single course of chemotherapy. Yamane *et al.*<sup>14</sup> showed that 18F-FDG uptake decreased as soon as one day after initiation of chemotherapy in patients with lymphoma.

In a more comprehensive study, Kostakoglu *et al.*<sup>15</sup> looked at the correlation between early response on PET scanning and ultimate outcome. Patients were scanned after the first cycle of chemotherapy and a statistically significant difference in progression-free survival for patients with positive versus negative PET scans was identified. This correlation was superior to that obtained with post-chemotherapy PET scans.

Hutchings *et al.* looked at two large groups of patients with Hodgkin's disease and tested the value of repeat PET imaging after 2 or 3 cycles of chemotherapy.<sup>16,17</sup> In their first series, 85 patients had interim PET scans repeated after 2 or 3 cycles of chemotherapy.

Only 3 of 63 patients with negative scans relapsed and 1 of 9 patients with minimal residual uptake relapsed. However, among 13 patients with positive scans, 9 progressed and 2 died. In their second study,<sup>17</sup> 77 patients underwent repeat imaging after 2 and 4 cycles of chemotherapy and again at the completion of chemotherapy. Only 3 of 61 patients with negative PET scans after 2 cycles of chemotherapy progressed, whereas 11 of 16 patients with positive scans progressed and 2 died.

These data suggest that interim PET scanning correlates strongly with prognosis. The potential value of this information is that treatment could be tailored more precisely to response, i.e., intensified among those who still have positive PET scans or reduced in patients who have an early conversion to a negative scan.

#### *Value in PET imaging for routine surveillance*

The fewest data are available with respect to the value of PET imaging as a routine surveillance study. Jerusalem *et al.*<sup>18</sup> studied its use in 36 patients scanned at the end of treatment and then every 4 to 6 months for 2 to 3 years. They identified 4 patients who relapsed during 5 to 24 months of followup. In all of these patients, PET imaging was the first study to suggest relapse. Relapse was never diagnosed first based on clinical examination, laboratory findings or computed tomography.

Spaepen *et al.*<sup>19</sup> reviewed the subject and concluded that if a patient has stage I-II HD and has a negative scan at the completion of therapy that no followup scans are indicated, whereas patients with initial stage III-IV disease would benefit from followup scans for several years. This question is a complex one which deserves further study, since the economic impact of surveillance PET imaging is significant and the benefit of identifying early relapse in this setting has not been defined. Indeed, investigators have questioned the value of even CT scanning as a routine followup study for patients with Hodgkin's disease.<sup>20</sup>

#### *PET imaging for radiation therapy treatment planning*

A novel application of PET scanning is its use in radiation therapy treatment planning. This concept has developed especially with the introduction of PET-CT imaging in which images from the PET scan are merged with the anatomic CT images. When patients are scanned in the treatment position this makes it possible to consider significant reduction in the size of radiation therapy fields. Involved fields may now be defined as PET positive regions as opposed to entire lymphoid regions. This will result in a significant decrease in the size of radiation therapy fields.<sup>21</sup> This

may be especially important for the pediatric patient who is at long term risk for secondary solid tumors, due to radiation exposure.<sup>22</sup>

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