AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST
The author(s) indicated no potential conflicts of interest.

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Reply to C. Gemici

We appreciate the interest shown in our report[1] by Gemici[2] and the opportunity to respond to his comments. He published an excellent review article on tumor lysis syndrome (TLS) in 2006.[3] He suggested that our patient may not be the third reported instance of TLS caused by radiotherapy because three patients had already been cited in his report. However, as we mentioned, only adult patients were included in our report. If pediatric patients were to be included, there would be more than three instances before his review.[4]

He also pointed out the inappropriateness of urine alkalinization during treatment of our patient. It is true that routine use of urine alkalinization is not recommended in most instances because of the potential risk of worsening renal problems or neurologic manifestations of hypocalcemia,[5] although it seems not to have affected the clinical course of our patient. Therefore, as he described, physicians should be aware of this controversial issue during management of TLS. He also added that increasing the urinary flow rate is a better alternative than urine alkalinization. However, vigorous hydration with diuretics is not a matter of alternative choice because it is the single most important measure to treat TLS.[5] The only decision to be made would be whether to use additional urine alkalinization for management of TLS.

Finally, he mentioned that the daily fractionated dose in addition to total dose should also be considered. We agree on his opinion in the aspect that all reported patients with TLS had received $\geq$ 3 Gy of daily dose. He also suggested that TLS might develop later and at higher total dose if lower daily dose ($\leq$ 2 Gy) were to be used. However, it is uncertain whether lower daily dose can result in TLS because there has been no such report on the matter. The threshold of radiation dose leading to rapid cell destruction might exist even in radiosensitive tumor cells. For better understanding, more experiences regarding radiotherapy-induced TLS need to be accumulated.

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Development and Application of a Real-Time On-Line Blinded Independent Central Review of Interim Pet Scans to Determine Treatment Allocation in Lymphoma Trials

To the Editor: [^{18}F]fluorodeoxyglucose–positron emission tomography (PET) interpretation criteria in lymphoma have been recently established[1]; however, their application is restricted to end of treatment assessment.[1] By contrast, there is still no consensus on the interpretation criteria for interim PET. Several studies using variable criteria have demonstrated that early PET has a high prognostic value in non-Hodgkin's lymphoma and Hodgkin's lymphoma, suggesting that it could be used to guide therapeutic strategy.[2-4] Criteria have ranged from purely visual or quantitative to a mix of visual and quantitative, with some advocating a certain amount of minimal residual uptake being tolerated for defining PET negativity.[2-4] However, many difficulties arise in the consideration of whether the examination is positive or negative in the case of minimal residual uptake. Even with blinded assessment, readers may disagree especially with borderline or complex cases.[5]

Therefore, it is highly desirable to establish a reading procedure that synthesizes the opinions of several experts, potentially from different imaging departments, for reducing the impact of interobserver variability. A major limitation to this approach is the necessity to obtain the multiple interpretations in a clinically relevant time frame (typically less than 72 hours) in order to allow alteration of the therapeutic strategy during the chemotherapy regimen. For these reasons, the classic retrospective or local blinded independent central review is not applicable. Blinded independent central review in real time would be an ideal option, but there are three main hurdles: all sites must have the ability to transfer images to the central review without delay; the local site must cede the final decision to the central review,[5] and the required number of expert reviewers must be physically available at the central review site at short notice at all times.

The Groupe d'Etude des Lymphomes de l'Adulte (GELA) and Société Française de Médecine Nucléaire developed a dedicated network allowing online PET review for the recently started European Organisation for Research and Treatment of Cancer (EORTC), GELA, and Intergruppo Italiano Linfomi (IIL) Intergroup H10 trial (EORTC 20051).[6] The H10 study is a randomized Intergroup trial on early [^{18}F]fluorodeoxyglucose–PET scan-guided treatment adaptation versus standard combined modality treatment in patients with early stage Hodgkin's lymphoma. PET is performed after two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine chemotherapy (PET2). Pretreatment PET (PET1) is highly recommended, although not mandatory.

The cornerstone of the network is a multimodality workstation which allows side-by-side display of pre- and post-treatment PET/computed tomography (CT), as well as complete image processing, including standardized uptake values analysis. PET/CT volume files acquired on the various PET cameras (GEMS; Siemens Medical, Philips Medical, Suresnes, France) are stored in the workstation. The investigator sends through the network the PET/CT files and an optical form containing his masked interpretation. A central GELA server dispatches the raw data to the workstations of six experts in France and Belgium. The network is based on digital subscriber line Internet connections, using file transfer protocols. The Digital Imaging and Communications in Medicine data are anonymized, and the internet connection is encrypted. A typical complete file size of about 200 megabytes is sent in less than 30 minutes from one center to the other. The experts make their own independent image processing and interpretation, and send the optical scan report form with the result to the central server where an integrated computation of the seven interpretations (six experts plus the local center) is performed.

PET2 are binary interpreted as positive or negative. The final result (computation of the local and of two, four, or six experts' readings obtained within 72 hours) is then sent to the coordinating center where it is checked and verified by the coordinating nuclear medicine physician before being sent back to the investigator. The full process takes less than 72 hours. Expert readers are informed that they have to review a scan by e-mail or short message service. They can also control the online process in real time on a secure Web site.

From June 2007 to November 2008, PET from 312 patients enrolled by 52 GELA centers in the Intergroup H10 protocol were analyzed through the network. From these we have selected 166 consecutive patients whose examinations were all read by the same five experts' centers within 72 hours. Thirty-eight patients had no PET1, and all patients but 11 were scanned with PET/CT.

The first 76 PET2 were read using the strict Juweid's criteria.[1] The cumulative agreement between pairs of experts was 79% (95% CI, 75% to 81%). The interobserver variability assessed by unweighted κ statistics on the five experts was $\kappa = 0.48$ (95% CI, 0.42 to 0.54), which is a moderate agreement. In order to improve such values, refined criteria of positivity were adopted during a consensus meeting (ie, positivity confirmed on the nonattenuation corrected images). For the next 90 PET readings, a significant improved agreement between experts was observed (85% agreement; 95% CI, 83% to 87%; $\kappa = 0.63$; 95% CI, 0.58-0.64; $P = .0008$). On the whole group, 6% discordant PET2 readings were observed between the local site reader and the central review panel, 73% of which were modified from negative to positive. Importantly, a significantly higher interobserver agreement ($P = .0001$) was achieved when the readers could interpret side by side the PET2 with PET1 (n = 128) than without (n = 38): $\kappa = 0.57$ (95% CI, 0.53 to 0.60), 84% agreement (95% CI, 82% TO 86%), versus $\kappa = 0.47$ (95% CI, 0.39 to 0.56), 75% agreement (95% CI, 70% to 80%), respectively.

This central review online process based on a true PACS approach has many advantages: (1) fast and secure transfer of all PET/CT volume files in such a way that a single reader can evaluate the full set of exams; (2) similarity of processing and display for all the experts with a dedicated workstation allowing side-by-side display of basal and post-treatment PET whatever the PET device used for the acquisition; (3) no limitation of the number of observers with the possibility to include the local nuclear medicine physician in the review process and to weight the final result by the local interpretation; (4) independent and online central review; and (5) rapid synthesis of the results, compatible with clinical practice allowing the investigator to decide the therapeutic strategy within 48 or 72 hours. Moreover, this network allows those involved to follow online the interobserver performance and to harmonize the interpretations; our first analysis strongly favors a pretreatment PET to improve the interim interpretation.

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