^{18}F-FDG PET for Routine Posttreatment Surveillance in Oral and Oropharyngeal Squamous Cell Carcinoma

TO THE EDITOR: We read with great interest the recent article by Krabbe et al. (*1*), in which the authors prospectively evaluated the impact and timing of ^{18}F-FDG PET for posttreatment surveillance of oral and oropharyngeal squamous cell cancer. Forty-eight patients were included after completing their initial therapy with curative intent.

The patients underwent clinical follow-up and ^{18}F-FDG PET at 3, 6, 9, and 12 mo after initial treatment. Two nuclear medicine physicians evaluated the PET scans and were unaware of the findings of the current clinical follow-up. At the second, third, and fourth PET scans, the nuclear medicine physicians had access to all available clinical data at the time of the previous scans, including the results of the previous regular follow-up and of morphologic imaging but not of the regular follow-up at the time of the current scan. The PET findings were validated by histopathology or clinical follow-up and by imaging at 18 mo after initial treatment.

When 3- and 6-mo posttherapy results were combined, ^{18}F-FDG PET was found to have detected malignancy in 16 of the 18 patients in whom locoregional recurrences, distant metastases, or a second primary tumor had occurred. It is therefore no surprise that the clinical impact of ^{18}F-FDG PET is best between 3 and 6 mo after treatment. The authors demonstrated that the sensitivity, specificity, and accuracy of ^{18}F-FDG PET were irrespective of the timing of ^{18}F-FDG PET and had ranges of 93%−100%, 68%−76%, and 71%−79%, respectively, during the 4 PET scans (Table 6 of the article). The negative predictive value showed little change between the 4 PET scans, whereas the positive predictive value was overall higher at the 3- and 6-mo scans than at 9 and 12 mo after treatment (61% and 47% vs. 29% and 36%). These findings were surprising to us. We thought that the diagnostic accuracy and particularly the positive predictive value of ^{18}F-FDG PET scans should have been higher at 9 and 12 mo than at 3 and 6 mo because more clinical follow-up and radiographic results after previous PET scans were available for correlation. The results of previous clinical examinations and radiographic imaging after the PET scans at 3 or 6 mo after treatment would help improve the confidence and the accuracy of the later PET scan interpretations at 9 or 12 mo after treatment. The general impression is that, between the end of therapy and PET, there is a decline in false-positive rates that is associated with an increase in positive predictive values and diagnostic accuracy (*2,3*). The results of the current study, however, appear to be at variance with the general impression. The authors acknowledged that ^{18}F-FDG PET/CT was shown to have high accuracy at 12 mo after treatment, but they did not discuss the findings based on ^{18}F-FDG PET (without CT). We would appreciate a discussion by the authors in this regard.

We noticed that a considerable percentage (50%) of the false-positive findings either were due to mucositis (8/40, or 20%) or were of unknown anatomic substrate (12/40, or 30%). These findings, however, were not correlated with time of occurrence; thus, the readers could not appreciate the ^{18}F-FDG PET pattern of these false-positive findings. Further characterization of these pitfalls of ^{18}F-FDG PET might help identify and decrease the false-positive rates. We would appreciate information from the authors in this regard.

A false-positive finding was shown in Figure 2 that apparently was present in all 4 serial PET scans. Only images of the PET scans at 3 and 12 mo after therapy were shown, and the authors did not provide any clinical information on the location of the ^{18}F-FDG focus that turned out to be false-positive. On the basis of soft-tissue loss seen in the presented radiographic images of the figure, we assumed that the patient had a left tonsillar cancer. We also assumed that the false-positive finding was in the right tonsillar fossa. On the basis of these assumptions, the right tonsillar ^{18}F-FDG uptake was most likely physiologic, because bilateral tonsillar cancer is rare (*4*). Moreover, if the clinical examinations and neck CT and MRI findings were not suggestive of tumor, the ^{18}F-FDG uptake in the right tonsillar fossa should have been interpreted as physiologic in the 6-, 9-, and 12-mo scans. We would appreciate the authors' comments on this specific case, with inclusion of the neck images of the 4 serial PET scans.

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REPLY: We would like to thank Nguyen and colleagues for their letter and the 3 questions they have raised after reading our paper (*1*): first, why the positive predictive value is higher at the 3- and 6-mo scans than at 9 and 12 mo; second, how the false-positive findings relate to the time of occurrence; and third, what clinical information we can present about the false-positive finding illustrated in Figure 2 of our paper.

Regarding the first question, we described a decline in positive predictive value during the 4 PET scans. The general impression

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of Nguyen et al. is that the false-positive rate declines with the interval between the end of therapy and PET and that such a decline would be associated with an increase in positive predictive value and accuracy. However, in their argument, they neglect the fact that the positive predictive value is dependent on the prevalence of malignancy. Despite a rather constant false-positive rate for the PET scans (9, 9, 10, and 7 for the 3-, 6-, 9-, and 12-mo posttreatment scans, respectively; Table 6 of our article), the positive predictive value decreased because the number of true-positive findings decreased. Patients with a malignancy detected by PET did not undergo subsequent scans.

However, we understand the surprise of Nguyen et al., who expected a decline in false-positive rate with the interval between the end of therapy and PET. They state 2 arguments. First, the accuracy of PET increases with the interval between the end of therapy and PET. We agree, because possible therapy sequelae could interfere with PET. However, this impression is valid only for a relevant period after treatment (3–4 mo). Therefore, we performed the first PET scan 3 mo after treatment (Discussion, paragraph 2, of our article). Our results suggest that PET 3 mo after treatment is not influenced significantly by posttreatment effects because no significant differences existed in sensitivity and specificity. Second, Nguyen et al. state that the results of previous clinical examinations, radiographic imaging, and PET scans would help to improve the confidence and accuracy of the later PET interpretations, 9 or 12 mo after therapy. In a clinical situation, this is correct. However, because of the design of our study, the nuclear medicine physicians could not neglect the focal hot spots in the study if no explanation (e.g., a benign finding) could be found for the uptake. They scored these hot spots as malignant until proven otherwise (as we discussed in our article), probably resulting in a higher rate of false-positive results than would occur in a clinical situation.

Regarding the second question of Nguyen et al., about how false-positive findings related to the time of occurrence, we could not demonstrate a pattern although we had expected to find one.

Regarding the third question, asking for clinical information on the false-positive finding illustrated in our Figure 2, that figure is an example of a false-positive finding that was unexplained by any anatomic substrate. The patient had a T4N2c squamous cell carcinoma of the left maxillary tuber treated with a combination of surgery and radiotherapy. The false-positive hot spot on the subsequent PET scans was indeed located contralaterally. A contralateral malignancy is rare. However, under our protocol the nuclear medicine physicians were not allowed to neglect the high focal ^{18}F-FDG uptake and scored it as malignant. Through our methodology, we tried to create a worst-case scenario in the follow-up and thus accepted a higher chance of false-positives. The scan 6 mo after treatment showed higher ^{18}F-FDG uptake than the scan 3 mo after treatment. The scan 9 mo after treatment showed ^{18}F-FDG uptake equal in size and intensity, but a new focus of uptake was seen at level 5 on the right side. Finally, the scan 12 mo after treatment showed uptake that had increased in size and intensity, and new focal uptake was seen right sublingually. Although the study results suggested malignancy, clinically this uptake was interpreted as physiologic. Additional diagnostics never proved malignancy.

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