value is shown as the minimum PSA in the reported range of PSA levels. It also appears that there was a mixture of patients with PSA relapse only and those with biochemical failure who had other imaging studies with abnormal findings (e.g., bone scan or CT). Despite the notion that ^{11}C-choline had a better detection rate than standard imaging, the important clinical question is what the detection rate of nonstandard ^{11}C-choline PET/CT is in the substantial number of men who present with PSA relapse only when standard imaging studies are negative (by definition). This question is important because currently, the most appropriate diagnostic and therapeutic maneuvers for asymptomatic men with biochemical failure remain undefined (*4–6*). It is suggested that the results of the report by Castellucci et al. would have been considerably more clinically useful if they had limited their data analysis (or had included the relevant subset of data analysis) to the PSA-relapse-only patients, who at this point cannot be deciphered from the published article. If ^{11}C-choline can provide unique information in this specific clinical setting, in which there is currently a void of a viable diagnostic imaging method, then important therapeutic decisions (e.g., salvage local vs. systemic therapy, or both) can be made earlier than when disease becomes apparent on standard imaging, potentially leading to improved patient outcome. Of course, validation of PET findings becomes challenging because by definition there are no standard imaging correlates (*7*). In such cases, tissue sampling, long-term follow-up, and content validity (e.g., pattern of detected lesions) may serve for validation. The second issue that needs attention is the definition of true-positive PET findings in this study, which was based on visual observation of any focal ^{11}C-choline uptake higher than surrounding background levels, correlation to other imaging studies (which we just argued would not be possible if we deal with a restricted definition of biochemical failure with no standard imaging evidence of disease), and regression with therapy or progression with no or ineffective therapy in subsequent scans. However, these validation criteria, as admitted by the authors, are the main limitation of their study. Perhaps these criteria are the reason for no false-positive results with ^{11}C-choline PET/CT in this study. For example, decline or resolution of focal uptake does not necessarily mean that a "malignant" lesion responded to treatment, because that lesion may have actually been benign and might have resolved (or improved) regardless of treatment for cancer. Such lesions are in fact false-positives but are labeled true-positives incorrectly simply because of the flawed validation criteria. Finally, it would have been helpful to know if there was a relationship between the PSA parameters and the chance of detecting only local recurrence, only metastatic disease, or both. Clearly additional studies with well-defined groups of patients, validation criteria, and endpoints would be needed in this important clinical setting.

REFERENCES

1. Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on ^{11}C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med.* 2009;50:1394–1400.
2. Krause BJ, Souvatzoglou M, Tincel M, et al. The detection rate of 11-C choline PET/CT depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:18–23.
3. Pound CR, Partin AW, Eisenberger MA, et al. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA.* 1999;281:1591–1597.
4. Moul JW. Prostate specific antigen only progression of prostate cancer. *J Urol.* 2000;163:1632–1642.
5. Mohile SG, Petrylak DP. Management of asymptomatic rise in prostatic-specific antigen in patients with prostate cancer. *Curr Oncol Rep.* 2006;8:213–220.
6. Scher HI, Eisenberger M, D'Amico AV, et al. Eligibility and outcomes reporting guidelines for clinical trials for patients in the state of a rising prostate-specific antigen: recommendation from the Prostate-Specific Antigen Working Group. *J Clin Oncol.* 2004;22:537–556.
7. Apolo AB, Pandit-Taskar N, Morris MJ. Novel tracers and their development for the imaging of metastatic prostate cancer. *J Nucl Med.* 2008;49:2031–2041.

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REPLY: It is our pleasure to answer the letter of Dr. Jadvar about our paper (*1*).

The diagnostic flow chart of patients with biochemical relapse after radical prostatectomy has yet to be defined with regard to either the most appropriate test to perform after a prostate-specific antigen (PSA) increase or the optimal timing for performing the test. It is probable that this lack is due to the fact that conventional imaging methods (CT, MRI, bone scanning, transrectal ultrasonography) have shown limited value in restaging of the disease, particularly when the PSA values are low (*2*). Furthermore, the optimal timing for performing imaging tests after biochemical failure is not well established yet because a balance has to be struck between the clinical need for early detection of relapse and the need to perform the tests when PSA values are high and, consequently, there is a higher probability of detecting relapse (*3*).

To find a possible solution to this problem, we have tried to clarify at least one aspect: the relationship between PSA values and PSA kinetics on the one hand and ^{11}C-choline PET/CT detection rate on the other hand. In response to the principal aim of our study, we can affirm that not only trigger PSA but also PSA kinetics influence PET/CT detection rates.

A secondary aim of our study was to compare the results of PET/CT and other imaging methods such as bone scanning or CT. In our study, of 130 patients who underwent bone scanning before PET/CT, 9 had positive bone scan results and 31 had positive PET/CT results. Furthermore, of 87 patients who underwent CT or MRI before PET/CT, 15 were positive for single lesions, whereas PET/CT detected disease relapse in 29 patients. We did not report PET/CT results for patients in whom the results of all conventional imaging methods were negative: nevertheless, in this context, 12 (21.4%) of 56 patients who showed negative results on conventional imaging showed positive findings on PET/CT.

The main limitation of our retrospective study is the validation of positive findings, because longitudinal follow-up with PET/CT or conventional imaging is affected by all the limitations identified by Dr. Jadvar. We tried to overcome this critical point by increasing the number of patients enrolled and thus trying to minimize the potential error. To our knowledge, our population is the largest ever studied with PET/CT after biochemical failure (190 patients). In our paper, we reported results on only a patient basis; however, in our population we detected 197 lesions in 74 of 190

positive patients. We cannot exclude with absolute certainty that a few lesions were erroneously categorized as true-positive; however, considering the high number of lesions analyzed and the high number of patients with multiple lesions, we can assume that the potential presence of a few false-positive lesions would not significantly affect the overall trend of the results.

Finally, to our knowledge this was the first published study taking into consideration the influence of PSA kinetics on PET/CT detection rate. As suggested by Dr. Jadvar, it would also have been useful to investigate the relationship between PSA kinetics and the site of the metastatic lesion. We accept with pleasure this suggestion, which would be the fruitful aim of an additional study.

In conclusion, with our work we hope we have been able to clarify at least some aspects of the possible flow chart to give additional information to clinicians using ^{11}C-choline PET/CT in patients with biochemical relapse. The principal objective here is to anticipate the detection of relapse and thus put clinicians in a position to take advantage of a more appropriate and broader set of therapeutic options.

REFERENCES

1. Castellucci P, Fuccio C, Nanni C, et al. Influence of trigger PSA and PSA kinetics on ^{11}C-choline PET/CT detection rate in patients with biochemical relapse after radical prostatectomy. *J Nucl Med.* 2009;50:1394–1400.
2. Choueiri TK, Dreicer R, Paciorek A, et al. A model that predicts the probability of positive imaging in prostate cancer cases with biochemical failure after initial definitive local therapy. *J Urol.* 2008;179:906–910.
3. Krause BJ, Souvatzoglou M, Tincel M, et al. The detection rate of 11-C choline PET/TC depends on the serum PSA-value in patients with biochemical recurrence of prostate cancer. *Eur J Nucl Med Mol Imaging.* 2008;35:18–23.

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