

REPLY: We thank Dr. Chiu et al. for their interest in our recent investigation on the impact of intravenous insulin on ^{18}F -FDG PET in diabetic cancer patients (1), and we would like to address their concerns.

The decision to use a 10.0 mmol/L threshold for insulin administration was based on the expected limited influence of this glycemia level on ^{18}F -FDG uptake and on the fact that it approaches the Km value of glucose transporter 3 (2). The Society of Nuclear Medicine guidelines state that most institutions reschedule the patient if the blood glucose level is greater than 8.3–11.1 mmol/L (3). The European Association of Nuclear Medicine does not recommend proceeding with an ^{18}F -FDG PET study when the glucose level in the blood exceeds 11.1 mmol/L (4). Choosing a higher threshold could reduce PET sensitivity. Choosing a lower threshold will increase the number of patients receiving insulin. We found no significant correlation between the initial glycemia and image quality. We disagree that “the set point to prescribe insulin in the study protocol of Roy et al. might account for their poor image quality.” Turcotte et al. used a lower threshold (7.0 mmol/L) and showed no significant increase in muscular uptake (5).

The guidelines of the Society of Nuclear Medicine mention that administering insulin can be considered, although the administration of ^{18}F -FDG would have to be delayed after insulin administration (3). This is in keeping with our finding that the interval between insulin and ^{18}F -FDG injection is a critical factor for image quality when insulin is administered. ^{18}F -FDG biodistribution was adequate in 75% of patients injected with insulin. This was not a “barely” adequate biodistribution as suggested by the author, but a normal or near-normal biodistribution. Administration of insulin in these patients allowed them to have a diagnostic ^{18}F -FDG PET study. Rescheduling PET scans is inconvenient for patients and delays investigation and treatment. Improvement of ^{18}F -FDG biodistribution in the remaining 25% of patients will certainly require systematic postponing of ^{18}F -FDG administration until at least 90 min after insulin injection.

We entirely agree with Dr. Chiu et al. that a better way to ensure adequate glycemia the day of the PET scan is to “do a ‘practice run’ by checking the patient’s blood glucose levels for at least 3 d before the ^{18}F -FDG PET appointment.” As we noted in the “Discussion” section of our article, “even with adequate recommendations, some patients will reach the department with elevated glycemia” (1). Calling our protocol a “risky strategy” seems exaggerated. We agree that intravenous insulin requires close medical surveillance, as provided for in our protocol. Six patients experienced hypoglycemia (9.5%), as defined by a glycemic level measured at 3.5 mmol/L or lower by glucometer. Moreover, the 2 patients who presented symptoms responded rapidly to oral glucose. Rescheduling PET is certainly a “no-risk” situation for the PET physician. However, some patients will require a few weeks before being able to reach adequate glycemia. The hypoglycemia risk associated with insulin use should always be balanced with the risk of delayed management. To address the issue of transcellular-shift hypokalemia, we recommended that patients with glycemia above 15 mmol/L should be rescheduled. We fully agree that there is nonuniform insulin sensitivity among hyperglycemic patients. The aim of this insulin administration, using a sliding scale, was to rapidly control the level of insulin before ^{18}F -FDG administration in hyperglycemic patients. It was never intended to manage diabetes or to replace any treatment regimen. In clinical PET practice, the insulin dose should be modulated according to patient profile.

In conclusion, we insist that our study sought to evaluate the safety and effectiveness of insulin administration to reduce glycemia in diabetic cancer patients who display elevated glycemia despite recommendations. We used a pragmatic approach to minimize the need to reschedule patients, reduce the risk of false-negative PET results due to hyperglycemia, and limit the hazards associated with insulin administration in patients with moderately elevated glycemia (10.0–15.0 mmol/L).

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Influence of Trigger PSA and PSA Kinetics on ^{11}C -Choline PET/CT Detection Rate in Patients with Biochemical Relapse After Radical Prostatectomy

TO THE EDITOR: The Italian investigators recently reported an interesting retrospective study on the effect of total prostate-specific antigen (PSA), PSA velocity, and PSA doubling time on the lesion detection rate of ^{11}C -choline PET/CT in 190 men who had been treated with radical prostatectomy and then presented with biochemical failure (1). Similar to a prior study (2), the general conclusion was that ^{11}C -choline detection rate increases as the values of the PSA parameters are increased, reflecting the underlying higher disease burden. In particular, the authors reported that the likelihood of lesion detection increases with a trigger PSA higher than 2.4 ng/mL or in those patients with PSA less than 2.4 ng/mL when PSA doubling time is lower than 3.4 mo or PSA velocity is higher than 1 ng/mL/y. However, additional information is needed to decipher the full potential clinical impact of the reported findings. First, the authors do not explicitly provide a definition for biochemical failure. It is assumed that a detectable serum PSA level of at least 0.2 ng/mL was considered as evidence for biochemical recurrence (PSA relapse), similar to that reported by Pound et al. (3), since this

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.

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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