Would Patient Selection Based on Both Calcitonin Blood Level and Doubling Time Improve ^{18}F-FDG PET Sensitivity in Restaging of Medullary Thyroid Cancer?

TO THE EDITOR: We read with great interest the paper from Ong et al. (*1*) in the April issue. This study was the first to investigate the potential impact of calcitonin serum blood level and doubling time on ^{18}F-FDG PET performance in the restaging of medullary thyroid carcinoma. On the basis of previously published papers dealing, first, with the influence of CA15-3 blood level and doubling time on PET performance in breast cancer patients with occult recurrence (*2*) and, second, with tumor markers in medullary thyroid carcinoma (*3,4*), several remarks may be addressed concerning the study of Ong et al.

Calcitonin doubling time could be calculated in 22 of the 38 PET scans in the series, and no significant difference was found in calcitonin doubling time between true-positive and false-negative PET findings.

Because the choice of a 1,000 ng/mL cutoff for calcitonin improved PET sensitivity from 62% to 78%, it would be interesting to investigate whether the likelihood of depicting recurrence is higher in patients with both a calcitonin blood level above 1,000 ng/mL (this value not being applicable in other institutions, as stated by the authors) and a short doubling time. It has been demonstrated in breast cancer that the combination of tumor marker blood level and doubling time may be useful in improving PET accuracy if patient selection is based on both criteria (*2*). The proportion of positive PET findings among patients with a low calcitonin blood level but short doubling time could also have been detailed, despite the fact that the sample was probably too small for definite conclusions to be drawn. For these purposes, a doubling-time cutoff of 6 mo could be applied, because this cutoff value has been proven to be a reliable prognostic factor in medullary thyroid carcinoma (*3,4*).

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REPLY: We thank Aide and Bardet for their comments on our article and would like to take this opportunity to briefly elaborate on the complex relationship between calcitonin, prognosis, and PET positivity.

In general, the probability for detecting sites of recurrent or metastatic disease on ^{18}F-FDG PET increases with tumor marker levels. This has been shown, for instance, in prostate cancer (prostate-specific antigen) (*1*), ovarian cancer (CA125) (*2*), colorectal cancer (carcinoembryonic antigen) (*3*), and breast cancer (CA15-3) (*4*). It is also clear that low tumor marker levels, in general, indicate low volume ("subclinical") disease recurrence, and oftentimes the findings of all imaging tests (structural or functional) are initially negative in these individuals. In fact, even with markedly elevated tumor marker levels, all imaging studies may show negative findings in some patients with, for instance, prostate cancer (prostate-specific antigen) or medullary thyroid carcinoma (MTC) (calcitonin). In patients with MTC who have a markedly elevated calcitonin level and negative imaging findings, it is not unusual to detect subcapsular liver metastasis on laparoscopy.

Our study (*5*) established that the sensitivity for disease detection by ^{18}F-FDG PET is higher in patients with calcitonin levels of more than 1,000 pg/mL. Aide and Bardet correctly point out that the use of different laboratory tests for calcitonin makes it difficult to apply this 1,000 pg/mL value universally. They suggest that using calcitonin doubling time, which also yields prognostic information, would circumvent this problem (a 100% increase is a 100% increase, regardless of the base point, units, or specific test kit, as long as the same test is applied all the time). Indeed, for many cancers evidence is now increasing that tumor marker doubling time is an important prognostic factor (*4,6,7*), and this is also true for MTC: In the study by Bardet et al. (*8*) in 65 patients with MTC, a calcitonin doubling time of less than 6 mo indicated a particularly poor prognosis, with 5- and 10-y survival rates of 25% and 8%, respectively. Similarly, in a retrospective cohort study of 120 patients with MTC, de Groot et al. (*9*) reported a worse clinical outcome among individuals with a calcitonin doubling time of less than 1 y. It is certainly plausible that a shorter calcitonin doubling time correlates with tumor progression and presumably also with lesion growth and metabolism. If the latter were true, one would expect a higher rate of PET-positive cases in individuals with shorter calcitonin doubling times.

We were able to calculate the calcitonin doubling time in 22 of the 38 PET scans in our study (12 true-positive, 9 false-negative, and 1 false-positive). Although there was a trend toward a shorter doubling time in PET-positive cases, the difference was not significant (6.6 vs. 12.1 mo), as may be explained by the relatively small patient sample and the considerable overlap in data points. When applying the suggested cutoff of 6 mo, we arrive at the following results: Among those with a doubling time of less than 6 mo, 4 scans were true-positive and 4 were false-negative. Among scans with a doubling time of more than 6 mo, 8 were true-positive and 5 were false-negative (1 finding was false-positive). For comparison, we also applied a cutoff of 1 y: Among patients with a doubling time of less than 1 y, 9 scans were positive and 4 were negative; among those with a doubling time of more than 12 mo, 3 scans were positive and 4 were negative. Thus, the cutoff of 1 y seemed to provide somewhat better sensitivity, but overall, the