Amino acid PET and clinical management of glioma patients

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In this issue, Yamane et al. [11] report a remarkable finding: Use of ^{11}C -methionine PET (MET PET) changed clinical management in 50% of their patients with brain tumours. One wonders whether this imaging technique is so much better than standard diagnostic procedures and whether usual clinical decisions without ^{11}C -methionine PET are so bad.

Let us consider first what ^{11}C -methionine offers. Several studies cited by Yamane and colleagues demonstrate indeed that this tracer provides very sensitive means to detect brain tumours, especially gliomas including the low-grade ones. This sensitivity appears to be the basis of the main finding by Yamane et al. that in up to 31% of cases active treatment was initiated based on MET PET while watchful waiting had been the preferred choice before. The opposite change was made much less frequently. Also, Yamane et al. found that in only 2 cases of 80 downgrading from active treatment to watchful waiting appeared to have been missing a viable tumour that, in retrospect, should better have been treated actively (one of them was lymphoma). They include that as a major concern in their conclusion while I think it is still consistent with high sensitivity of MET PET, at least for gliomas. Cited studies also suggest a reasonably good specificity of MET PET for differentiation of tumour from non-tumour lesions, although the evidence for that is somewhat limited and cases of high ^{11}C -methionine uptake have been reported in recent ischaemic and florid inflammatory

lesions [3, 8]. Overall, the diagnostic case for MET PET appears to be well founded and Yamane et al. make clinical use of that.

However, do we really have the evidence for changing clinical practice based on MET PET? We don't. Better treatment implies better outcome with respect to survival and quality of life. Evidence for that is sorely missing, and the paper by Yamane et al. does not contain relevant information in that respect. Progress in brain tumour treatment has been painfully slow, and in spite of some improvement in chemotherapy in malignant gliomas [9], prognosis for glioblastomas remains among the worst of all cancer types. On the other hand, survival times for low-grade gliomas have increased in published statistics [2], but most of the apparent improvement is probably due to the big step in diagnostic sensitivity and associated earlier diagnosis by widespread use of MRI (compared to CT) in these non-enhancing lesions. In fact, studies have shown that low-grade gliomas may remain stable over many years without disabling symptoms while active treatment may carry a risk of significant morbidity [7]. Also, evidence is missing that active treatment would prevent recurrence of these infiltrating lesions [4]. Clinical results are also inconclusive for active treatment of recurrent malignant gliomas. Thus, active treatment is not always the better choice for the patient—and we should not draw premature conclusions solely based on an improved ability for tumour detection.

Is there a way out of this dilemma? Obviously, we need to perform studies that consider the effect of changes in diagnostic procedures on the ultimate outcome. This is a big challenge because of the large number of variables involved, the complexity of clinical pathways and the time needed for proper follow-up. Nevertheless, a few observational studies have been considering the entire picture and

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they encourage cautious optimism [5]. It appears unlikely in the foreseeable future that an ^{11}C -labelled tracer, which depends on cyclotron production on-site, will be available broadly enough to be part of a comprehensive clinical study. ^{18}F -Labelled amino acids [6] may be more suitable for clinical use, and kinetic analysis may allow further differentiation [10]. We also cannot afford ignoring advanced MR techniques which also provide sensitive means to discriminate active tumour from non-tumour lesions [1], typically at considerably less cost. Overall these advances are good news for patients, and we should engage in studies taking into account all major factors that are relevant to them and provide evidence for improved clinical decision making.

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