Journal of Nuclear Medicine, published on June 30, 2016 as doi:10.2967/jnumed.116.178160

Appearances are often deceptive

A. Haug, H. Ilhan

Dear editor,

With great interest we have read the letter of Garin and colleauges [1]. Garin et al. question the results of our study, which showed only a moderate correlation of pre-therapeutic [99mTc]-MAA (MAA) SPECT and distribution of [90Y]-SIR-spheres in more than 500 patients [2]. Obviously, the assumption that a high MAA uptake is followed by a high [90Y]-microspheres uptake, which translates in a high dose to the tumor and, therefore, in a good response to radioembolization sounds straightforward and striking. However, also obvious assumptions have to be proven, even more as biology has taught us that least tumor-related issues follow simple mechanistic correlations. Garin et al. cite three studies and one review, which reported contradicting results in terms of a good correlation of MAA-uptake and treatment response [3-6]. However, most studies suggesting a good correlation of MAA SPECT and bremsstrahlung SPECT are dealing with hepatocellular carcinoma (HCC). HCC are somewhat different to secondary liver tumors in some aspects. HCC are in the majority highly perfused, have often distinct tumor feeding arteries and are either solitary or oligo-metastatic. These properties might account for the reported higher correlations in our view. Indeed, pre-therapeutic angiography in HCC is often done in a selective fashion with injection of MAA into tumor feeding arteries and not into the right and left hepatic artery, as done in most secondary liver tumors due to the disseminated distribution of lesions. Injection of both MAA and microspheres mainly in tumor feeding arteries makes discrepancies between MAA and microsphere distribution less likely. Consequently, in our study the correlation of MAA and microsphere uptake was markedly higher in HCC ($r=0.398$, $P<0.001$) as compared to secondary liver tumors such as metastases from colorectal cancer ($r=0.22$; $p<0,001$), breast cancer ($r=0.308$; $P=0.001$) and neuroendocrine tumors ($r=0.197$; $P=0.008$) [2]. The lower correlation of MAA and microsphere uptake in non-HCC liver tumors is supported by several studies, partly with high numbers of included patients. Ulrich et al.

found no significant correlation between response and MAA uptake in 66 patients suffering from colorectal liver metastases [7]. Also Wondergem et al. reported about significant differences in MAA and microspheres uptake [8]. Finally, our group has reported in another study, that cholangiocellular carcinoma with a high MAA uptake did not differ from those with low uptake in terms of survival [9]. Cholangiocellular carcinoma with a high MAA uptake showed even a trend towards shorter survival (51 weeks) than those with low uptake (median survival not reached). Similar results are reported by two other studies [10, 11]. These finding underline the complexity of tumor biology. The delivered tumor dose seems to be only one factor for the prognosis of patients treated with radioembolization; not considering other important factors influencing the prognosis of tumors significantly means to ignore the complexity of cancer. Neo-angiogenesis is for sure a hallmark of cancer aggressiveness and prognosis [12, 13], which might even outweigh the higher achievable dose in those tumors.

A second important issue related with the discrepant results reported in several studies is the used kind of microspheres. While glass microspheres do not have a relevant embolizing effect, resin microspheres are -due to the much higher amount of injected particles- embolizing a significant part of the vessels in the treated part of the liver and, therefore, the blood flow is changing over time. In a significant proportion of patients of up to 20% the treatment has even to be stopped prematurely because of treatment induced stasis [14]. Of course this embolizing effect is very likely to change the blood flow and spheres distribution over time.

Garin et al. have identified differences during the diagnostic as compared to the therapeutic angiography such as catheter position and vasospasm as a probable reason for the reported low correlation. The vast majority of all angiographies in our study have been performed by the same experienced interventional radiologist with more than 20 years of experience. Therefore, differences in the catheter position cannot be ruled out with certainty, but seem quite unlikely and cannot be considered as a major confounding issue. This is also supported by the findings of Ulrich et al., who did not find any correlation of catheter position, MAA uptake and therapy response [7]. Secondly, we experienced only a very limited number of vasospasms during angiography. We did coil embolization

of aberrant vessels only in a limited proportion of patients and only during therapeutic angiography [15]; therefore, vasospasms caused by prolonged diagnostic angiographies cannot explain the fact of low MAA uptake and higher microspheres uptake as proposed by Garin et al. Further on, in most cases 1-3 weeks are between diagnostic and therapeutic angiography. Considering the highly dynamic biology of cancer it is not likely that tumor perfusion stays stable over time, which is also a factor impairing the comparability of MAA and microspheres uptake.

In conclusion, our study with up to now by far the highest number of included patients showed a significant, but moderate correlation between MAA and microspheres uptake in various tumor entities. Despite the fact that of course many factors can influence the respective tumor uptake, due to the high number of reported patients the results have to be registered as evidence that MAA is no good indicator for the distribution of resin microspheres. These results, however, should not impair the clinical value and relevance of MAA scintigraphy prior to radioembolization, particularly with regard to identification of aberrant vessels and high liver-lung shunting.

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