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General review

Is there a place for nuclear medicine in the radioembolization of liver tumors?

Y a-t-il une place pour la médecine nucléaire dans la radioembolisation des tumeurs hépatiques ?

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Abstract

This is purposely an ultraprovocative title for the broad nuclear medicine community (including radiophysics and radiopharmacy) which leads us to ask questions about how we should correctly use ^{90}Yttrium (MSY90) microspheres in the treatment of liver tumors.

Keywords: Nuclear medicine; Radioembolization; Liver tumor

Résumé

Ce titre volontairement ultraprovocateur pour la communauté large de médecine nucléaire (radiophysique et radiopharmacie incluses) doit nous amener à nous poser des questions sur la façon dont nous devrions nous approprier l'utilisation des microsphères marquées à l'yttrium 90 (MSY90) dans le traitement des tumeurs hépatiques.

Mots clés : Médecine nucléaire ; Radioembolisation ; Tumeurs hépatiques

1. Introduction

For certain people, the place of nuclear medicine is limited to the ordering of therapeutic doses, their storage and the management of waste materials. The term ''radioembolization'', which remains currently used today, is symptomatic because it inevitably refers to chemo-embolization, technique where in addition to chemotherapy involves macroscopic arterial embolization which is not the case with ^{90}Yttrium (MSY90). The term selective internal radiation (SIR) therapy or vectorized internal radiation (VIR) therapy should be used by everyone.

Moreover, it is sufficient to look at the design of the randomized phase 3 trials currently being conducted, in order to realize that today the weight of our discipline is comparatively insignificant and for two principle reasons.

First, contrary to good practice, patients with contraindications to one of the two treatment arms are included in these trials without receiving the treatment that is in fact being studied. Simply stated, patients with an excessive pulmonary shunt or digestive shunt, which correspond to absolute contraindications for the use of microspheres (MS), should

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not be included in the study. This concept of absolute contraindication is obvious for us nuclear medicine physicians; however, this situation is usually analyzed differently by clinicians who generally consider the presence of a major digestive or pulmonary shunt as a failure of intention to treat. This is completely erroneous, as a failure to treat is an inability to treat a patient once the treatment indication has been validated. In the cases of MSY90, this corresponds to the patients who cannot receive the treatment although the patient has been previously validated beforehand as to their absence of an excessive lung shunt or digestive shunt during the diagnostic angiography. Furthermore, the patient also undergoes a hepatic perfusion scintigraphy examination for human serum albumin macroaggregates labeled with ^{99m}Tc-macroaggregated albumin (MAA). In the Sirflox trial, whose disappointing results were published this year (there was no significant impact of MSY90 on progression-free survival) [1], 7% of patients were incorrectly included in the study due to the presence of a lung or digestive shunt (if the non-ambivalence clause had been respected), significantly biasing the results of the trial. Within the framework of a non-resectable hepatocellular carcinoma (HCC), this proportion of patients was even higher. In a study comparing the frequency of pulmonary shunts, only 5% of patients with metastases had an elevated lung shunt, $>$ 15% compared with 28% in HCC [2].

Secondly, despite the fact that this is an internal radiotherapy technique, in ongoing phase 3 trials, no dosimetric approach taking into account the tumor dose and dose to the critical organs is used, while the dosimetric tools are available and in the case of HCCs with the use of resin MS, for example, a dose-response relationship with a threshold of 120 Gy was identified more than 20 years ago [3]!!!

2. In reality, the place of nuclear medicine in the SIR of liver tumors is fundamental

In addition to the regulatory law of authorization for the possession and use of radiolabelled MS which are the responsibility of the nuclear physician and which alone are sufficient to justify this crucial role. We also have a major role to play in the medical management itself with performing MAA scintigraphy at least on two levels: patient selection and definition of delivered doses. The visual or dosimetric analysis of the post-therapeutic scintigraphy is equally an important point of the management that we are responsible for carrying out.

2.1. Patient selection

SIR with the MSY90 is a multidisciplinary technique where clinicians (oncologists, hepatologists, and surgeons), radiologists and nuclear physicians have a role to play directly in the selection of patients. We search for patients at major risk of complications with the measurement of the lung shunt and the search for digestive shunts. We equally have a role to play in evaluating tumor targeting permitting to predict successful treatment.

Evaluation of the lung shunt is our responsibility. Classically, it is based on a quantification of MAA planar acquisitions. Different studies have recently shown an overestimation of a factor of about 2 for the lung shunt, measured from planar acquisitions compared to SPECT/CT scan [4,5]. Efforts must therefore be made to improve the quantification of the lung shunt because we know today that we have probably mistakenly excluded patients from this therapeutic approach due to an overestimation of the lung shunt.

The search for a digestive shunt is also a major point in the selection of patients for which the SPECT/CT holds an important place. Different studies have shown the superiority of SPECT/CT in the sensitive detection of digestive shunts compared to planar acquisitions [6,7].

However, the identification of a gastroduodenal uptake in connection with a digestive shunt may be difficult and lead to excessive diagnostic errors. In fact, the rate of gastroduodenal uptake identified in SPECT/CT varies from less than 5% [8] to more than 20% [6,7] and can exceed 30% [9]. From 20% to 30% of gastroduodenal uptake in relation to a digestive shunt not detected on arteriography is simply not possible and probably related to diagnostic errors in the interpretation of SPECT/CT.

In fact, certain uptakes of vascular origin at the level of the hepatic hilum may be misinterpreted as being of duodenal origin. These uptakes can be found at the level of the hepatic artery, probably at the level of the microlesions generated by the catheter [8], embolization coils [6,8] and thromboses of the portal vein [8]. They are frequent and were found in 20% of cases in our experience [8]. The presence of co-registration errors between the CT and SPECT may also be responsible for diagnostic errors [8]. The interpretation of SPECT/CT must therefore be particularly rigorous, it requires a good knowledge on the part of the isotopic physician to interpret the diagnostic CT scan and often, it is necessary to confront our interpretation with that of the radiologist (was there any doubt about the arteriography on the presence of a digestive branch? Difficult arteriography with risk of arterial micro lesion?, etc.) so as not to consider of the uptake of gastroduodenal origin of other origin and wrongly exclude treatment from a patient who is a potential candidate.

Tumor targeting is also assessed by SPECT/CT. Even with the use of 3D angiography acquisition, the evaluation of tumor targeting may be contradictory between angiography and SPECT/CT, a striking example is shown in Fig. 1. These differences may be explained, in particular, by the use of a different injection technique between the iodinated contrast agent, the injection of a large bolus volume at a high flow rate, or the MAA scintigraphy with a slow infusion of a small volume, recommended over a period of 20 to 30 seconds to best mimic the injection of radiolabelled MS [10]. Again, the results of SPECT/CT must be compared with those of arteriography in order to modify the treatment position to optimize tumor targeting.

Similarly, for patients presenting with portal thrombosis, targeting of this thrombosis by MAAs is an important point to