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Extravasation of diagnostic radiopharmaceuticals, a wolf in sheep's clothing?

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Invited Perspective on the paper by Parihar et al. *(2)*

Radiopharmaceutical extravasation (RPE) is occurring worldwide on a frequent basis. As we have reported in our 2017 literature study, the evidence on clinical consequences of RPE is scarce.(*1*) Studies we found at that time only described clinical follow up in a handful of case reports, mostly on incidental therapeutic extravasation. Parihar and colleagues present the results of their retrospective study focusing on clinical outcome after RPE.(*2*) The work currently presented, reports clinical follow up in 96 patients in which RPE occurred out of 31.679 screened reports of patients who underwent a whole body bone scintigraphy (WBBS) using 99mTc-MDP.

One of the conclusions of our work was that adverse events following tracer extravasation might be underreported. On the other hand, if clinical consequences of diagnostic tracer extravasation would occur in significant numbers, especially with severe or even moderate tissue reactions as a result, more reports would have been expected to be published. This study finally adds objective data of a real world setting to support this hypothesis. The median follow up duration of 18.9 months further precludes late onset adverse events.

The current study evaluated scan reports of one single center over the time of 12 years to detect cases of RPE. This is certainly a limitation of this study as correctly stated by the authors. An alternative approach would have been a study aimed at detecting extravasation visually on the scans. This would indeed have given a more reliable figure of the frequency of RPE, which seems to be on the very low end in this

study.(*2*) As many of us routinely observe in daily clinical practice, many scans already show minor tracer infiltration, which is also illustrated by other studies such as cited by the authors.(*2*) Even one of the illustrated cases only shows minor tracer extravasation, which can be expected to occur in relatively high numbers in WBBS. The used approach does have the tendency to focus on large tracer extravasations which captured the attention of the reading physician and which prompted clinical follow up. One would obviously expect more severe adverse reactions in more prominent RPE. Despite a tendency for lower sensitivity to include tracer extravasation, the study design after all does focus on more extended extravasation cases where clinical consequences of RPE, would be most probable.

Being a retrospective study, patients were not actively checked for any symptoms at planned follow up checkups. The study also potentially misses patients that presented with mild symptoms to the home practitioner or other healthcare professionals.

The authors' conclusion that clinical adverse events following tracer infiltration are rare, remains plausible and is in line with our earlier findings based on literature and the experience we have in our own clinical setting. However, the methodology of the current study analyzing only reported cases, inherently does not rule out RPE completely, notably in cases where it was not reported, therefore potentially missing clinical cases with adverse reaction.

The discrepancy between extravasation frequency reported in current study, as opposed to frequencies reported by earlier studies of retrospectively investigated WBBS and 18F-FDG PET scans for tracer extravasation also emphasizes a current hiatus in the definitions and raises the question how a clinically significant RPE should be defined.

Of further notable interest is that in three out of four RPE cases, for which an event directly attributable to RPE was documented, already extravasation of iodinated contrast for a contrast enhanced CT earlier on the day was documented. This happened despite the standard procedure for intravenous tracer injection in operation in their medical center, that is carefully explained by the authors, including a patency check by confirming adequate blood return. Circumstances possibly leading to the reuse of an injection site at which extravasation occurred are not elucidated. It does emphasize the importance of a proper patency check and to refrain from reusing an injection location which recently was subject to extravasation.

The authors mention that from September 2017 on, all tracer injections were performed using a small gauge butterfly needle for intravenous injections of 99mTc-MDP, as opposed to a straight stick technique injection. Unfortunately, no information is given on the frequency of RPE before and after the change in technique.

Studies of RPE cases that report clinical follow up in other abundantly used tracers such as other ^{99m}Tc-labeled tracers, ^{18}F-FDG or ^{68}Ga-labelled tracers, are still missing. The same is true for all recently new diagnostic tracers being introduced to the clinic.

A dose estimation assuming the worst case of no clearance of the extravasated radiopharmaceutical in tissue would result in doses that have shown local deleterious effects in external beam irradiation. However, the real world looks different since there is usually rapid and effective clearance via the

lymphatic system. That is the reason that reports on serious adverse events are scarce. Only one recent study has reported some cases. They summarize several cases with multiple registered clinically relevant symptoms; however, the cases are not presented with enough detail to find a causal relation to the extravasation of the tracer.(*3*)

The work of Parihar and colleagues further supports the hypothesis that clinical consequences of RPE in general are very rare. We encourage that cases of clinical extravasation are handled according to a standardized operating procedure, such as the local procedure we use and published earlier, in which cases are documented.(*1*) These data can then be aggregated and published such as Parihar and colleagues have done. Care should also be taken to image quality, which can suffer from extravasation. Although in only three out of 122 cases reported by Parihar et al. a new WBBS was ordered, for ^{18}F-FDG-PET it has been proven earlier that standardized uptake values can considerably vary between scans with and without RPE.(*4*)

Furthermore, in the current times of expansively growing use of therapeutic radioactive compounds, in our opinion attention should be broadened to include clinical consequences of RPE in radioligand therapy. Since our earlier literature study, some additional cases of therapeutic radiopharmaceutical extravasation of ^{177}Lu-labelled compounds have been reported.(*5-9*) None of these report any serious clinical consequences, however. Furthermore, the EANM dosimetry committee recently published a guideline on dosimetry of ^{177}Lu-labelled somatostatin and PSMA targeting ligands, in which some practical points are given in the dosimetric approach of a therapeutic RPE case. They also stress that despite regular use of these compounds, no serious adverse events have been observed after tissue extravasation, which can probably be attributed to rapid clearance from the extravascular space. Estimated absorbed doses to the surrounding tissues did no exceed the dose threshold for ulceration and desquamation.(*10*) These results suggest that a case of ^{177}Lu-labelled compound extravasation should be treated conservatively, although further research is necessary to support this hypothesis.

Large randomized controlled trials (RCT), notably the NETTER-1 and VISION trials that have recently been performed on new therapeutic radiopharmaceuticals, do not report on extravasation. (*11,12*) We encourage that future large RCT's will actively monitor and report on RPE, preferentially incorporating a detailed standard operating procedure for RPE in the study protocol, including prolonged clinical follow up in case of RPE.

In conclusion, RPE is a relatively common event, depending on the definition as stated above. The work by Parihar et al. adds more evidence supporting our earlier conclusion that RPE in abundantly used ^{99m}Tc, ^{123}I, ^{18}F and ^{68}Ga diagnostic tracers do not require intervention. More research is nevertheless needed, with an emphasis on new diagnostic tracers and therapeutic radiopharmaceuticals.

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