Extravasation of Diagnostic Radiopharmaceuticals: A Wolf in Sheep's Clothing?

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Radiopharmaceutical extravasation (RPE) is occurring worldwide on a frequent basis. As we reported in our 2017 literature study, the evidence on the clinical consequences of RPE is scarce (*1*). Studies we found at that time described clinical follow-up in only a handful of case reports, mostly on incidental therapeutic extravasation. In this issue of *The Journal of Nuclear Medicine,* Parihar and colleagues present the results of their retrospective study focusing on clinical outcome after RPE (*2*). In their review of 31,679 screened reports of patients who underwent whole-body bone scintigraphy using ^{99m}Tc-methylene diphosphonate, they report clinical follow-up in 96 patients in whom RPE occurred.

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

The current study evaluated scan reports of a single center over 12 y to detect cases of RPE. Only scanning the reports 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*). One of the illustrated cases even shows only minor tracer extravasation, which can be expected to occur in relatively high numbers in whole-body bone scintigraphy. The used approach does have the tendency to focus on large tracer extravasations, which captured the attention of the reading physician and 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 did, after all, focus on more extended extravasation cases in which clinical consequences of RPE would be most probable.

Since the study was retrospective, patients were not actively checked for any symptoms at planned follow-up checkups. The study also potentially missed patients who presented with mild symptoms to the home practitioner or other health-care professionals.

The authors' conclusion that clinical adverse events after tracer infiltration are rare remains plausible and is in line with our earlier findings based on the literature and our experience 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 for which it was not reported, therefore potentially missing clinical cases with an adverse reaction.

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

Of further notable interest is that in 3 of 4 RPE cases for which an event directly attributable to RPE was documented, extravasation of iodinated contrast medium for a contrast-enhanced CT scan earlier on that day had already been documented. This happened despite the standard procedure for intravenous tracer injection in operation in the authors' medical center—a procedure 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 that recently was subject to extravasation.

The authors mention that from September 2017 on, all intravenous injections of ^{99m}Tc-methylene diphosphonate were performed using a small-gauge butterfly needle 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-labeled tracers, are still missing. The same is true for all new diagnostic tracers recently being introduced into the clinic.

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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 found some cases. The investigators 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 tracer extravasation (*3*).

The work of Parihar et al. further supports the hypothesis that clinical consequences of RPE in general are very rare. We encourage handling of clinical extravasation cases 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 as Parihar and colleagues have done. Care should also be taken with image quality, which can suffer from extravasation. Although in only 3 of 122 cases reported by Parihar et al. was a new whole-body bone scintigraphy ordered; for ^{18}F-FDG PET, it was proven earlier that SUVs can vary considerably between scans with and without RPE (*4*).

Furthermore, in the current time of expansively growing use of therapeutic radioactive compounds, we believe attention should be broadened to include clinical consequences of RPE in radioligand therapy. Since our earlier literature study, some additional cases of therapeutic RPE of ^{177}Lu-labeled compounds have been reported (*5–9*). None of these reports indicate any serious clinical consequences, however. Furthermore, the European Association of Nuclear Medicine dosimetry committee recently published a guideline on dosimetry of ^{177}Lu-labeled somatostatin and prostate-specific membrane antigen–targeting ligands, in which some practical points are given in the dosimetric approach toward a therapeutic RPE case. The committee also stresses that despite regular use of these compounds, no serious adverse events have been observed after tissue extravasation, as can probably be attributed to rapid clearance from the extravascular space. Estimated absorbed doses to the surrounding tissues did not exceed the dose threshold for ulceration and desquamation (*10*). These results suggest that a case of ^{177}Lu-labeled compound extravasation should be treated conservatively, although further research is necessary to support this hypothesis.

Large, randomized controlled trials, 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 future large, randomized controlled trials to 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 cases of RPE.

In conclusion, RPE is a relatively common event, depending on the definition. 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 does not require intervention. More research is nevertheless needed, with an emphasis on new diagnostic tracers and therapeutic radiopharmaceuticals.

DISCLOSURE

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