Implementation of dosimetry for molecular radiotherapy; results from a European survey

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1. Background

Treatments with radioactive nuclides, also known as molecular radiotherapies (MRTs), have been rapidly increasing over the last years. The aim is to deliver an absorbed dose to the region of disease, leading to a therapeutic effect, while minimising absorbed doses to non-target tissues.
tissues. While some treatments, including radioactive iodine (Na\(^{131}\)I), have been in routine use since the 1940s [1,2], many new carriers and radionuclides have been developed for MRTs in the last decade. A recent review found that 72 radionuclides have been investigated for molecular radiotherapy [3]. The majority of current treatments employ beta-emitting radionuclides, although the use of alpha-emitters has also increased since the approval of \(^{223}\)RaCl\(_2\) (Xofigo®) in 2013 [4].

It is possible to follow the distribution of the radiopharmaceutical over time by using imaging-based methods like gamma cameras or position emission tomography (PET) to detect emitted photons, and/or other methods such as measurements acquired with external probes or from blood samples. This allows for determination of the absorbed dose rates in real time, and hence the absorbed doses to tissues and targets of interest can be calculated. Recent developments in theragnostic approaches, with the use of companion diagnostics to inform uptake and retention of the radiotherapeutic, can also enable pre-treatment planning based on the absorbed doses to be delivered.

For external beam radiation therapy (EBRT), the treatment delivery is planned for each individual patient considering the healthy tissue complication probability for the absorbed dose to these tissues, as well as the tumour control probability for the region of disease. Routine implementation of dosimetry for MRT has traditionally varied significantly between treatments, countries and centres, with many therapeutics registered as a fixed dosimetry product. However, since 2018 the European Council Directive 2013/59/Euratom mandates individual planning and verification for absorbed doses delivered to target regions, specifying that absorbed doses to non-target tissues should be kept as low as reasonably achievable [5]. In 2015, a survey was conducted to assess the implementation of dosimetry for MRT [6]. Across all types of MRT, a median of 36% of responders reported that some form of dosimetry was included for all or the majority of patients [6]. However, large variations were observed both between the responding centres and between MRTs. Since then, several recommendation papers have been published on the interpretation and implementation of Article 56 of the Council Directive 2013/59/Euratom [7–9], and the directive should be adopted in national legislations. Moreover, new radiopharmaceuticals have been introduced. The aim of this work was to conduct a new survey, examining the development of dosimetry implementation over time since the previous survey, and to investigate current dosimetry methodology and medical physicist staffing levels.

### 2. Methods

#### 2.1. Survey design

This survey on Radionuclide Therapy Dosimetry Implementation was developed by a workgroup of the Special Interest Group of Radionuclide Internal Dosimetry (SIGFRID) [10], part of the European Federation of Organisations for Medical Physics (EFOMP). The initial study was open for treating centres between April and June 2022. The questions focused on treatments and dosimetry performed in the years 2020–2022. It was written in English and implemented in a web-based questionnaire (Google Forms). An introductory page explained the survey aim and gave an overview of the included therapies (Table 1). All participants agreed to anonymised publication of the responses.

The first section of the survey intended to gather general information on the use of MRT and, if applicable, dosimetry, asking about the availability of medical physicists working at/for the clinical department involved in MRT, the number involved in dosimetry calculations, potential participation in clinical trials involving dosimetry, availability of software for dosimetry, and quality control routines.

The second part of the survey included questions for each of the therapies defined in Table 1. If responders indicated that the specified therapy was indeed performed at their centre, they were asked about the annual frequency and whether dosimetry was performed for this treatment. If the response to the latter question was ‘yes’, additional
questions were asked regarding dosimetry: whether it was used for treatment planning and/or verification, whether it was performed for normal tissues at risk and/or regions of disease, which type of dosimetry was performed (e.g. 3D voxel based, 2D/3D mean absorbed dose, non-image-based) and whether a medical physicist was involved in the dosimetry calculations.

A complete overview of the survey questions is presented in Supplementary Materials 1.

2.2. Analysis

All entries into the web-database were exported to an Excel spreadsheet and curated manually. This process included merging records and removing duplicate entries and inconsistent data. Results were then analysed for the complete database as well as for selected country-level questions.

3. Results

Initially 203 responses were received, of which 195 were from centres performing MRT (Fig. 1). However, some of these responses were incomplete and therefore not suitable for analysis. A total of 173 responses were suitable for analysis, geographically distributed over 27 countries in Europe (Fig. 2, overview per country). Of these, 146 centres indicated that they performed dosimetry and completed the corresponding questions. Questions related to dosimetry software and quality control were completed by 113 responders.

The most common MRTs performed by the responders were $^{131}$I-based treatments for thyroid diseases and thyroid cancer, and $^{223}$Ra RaCl$_2$ (Fig. 3). This applied to both the total number of centres, as well as the annual frequencies. Other common therapies included $^{177}$Lu-based treatments (conjugated with somatostatin analogues for neuroendocrine tumours and prostate-specific membrane antigen (PSMA) for prostate cancer) and $^{90}$Y microsphere treatments for liver malignancies. Some therapies were performed in less than 15% of the centres, and typically...
with less than 10 treatments annually. This included $^{90}$Y-somatostatin analogues for treatment of neuroendocrine tumours, $^{166}$Ho microspheres, $^{[89m]Sr}SrCl_2$ (Metastron®), $^{225}$Ac-PSMA for prostate cancer, $^{177}$Lu/$^{90}$Y-CXCR4 for haematological neoplasms, $^{177}$Lu-lilotomab satratoxetan (Betalutin®) for non-Hodgkin’s lymphoma and a $^{188}$Re-based treatment for basalomas and squamous cell carcinomas. An overview of all other treatments can be found in Supplementary Materials 2, Table 1. All of the treatments mentioned were performed in a limited number of centres (1–3). For all but the $^{225}$Ac-based treatments, some form of dosimetry was performed (Supplementary Materials 2, Table 2).

84% of the responding centres indicated that they performed dosimetry for at least one type of MRT, and 97% of these centres had a medical physicist available to support dosimetry (Fig. 5). Among centres not performing any form of dosimetry, approximately 1/4 indicated that
they did not have a medical physicist available. The available full-time equivalent (FTE) of medical physics staff available to support dosimetry differed largely per country, with a mean availability between 0 and 1.0 FTE across all countries (Fig. 6).

It was found that some therapies are generally performed using dosimetry for treatment planning and/or verification (especially treatments with radioactive microspheres), while other therapies are more commonly delivered without the use of dosimetry, as can be seen from Figs. 7 and 8. Fig. 9A indicates whether dosimetry is performed for normal tissues at risk and/or for regions of disease for each therapy.

For each therapy, the distribution of dosimetric approaches (image-based 2D or 3D mean absorbed dose, 3D voxel dosimetry and/or non-imaging based approaches such as external probe measurements or blood draws) utilized across European countries can be found in Fig. 9B. The involvement of medical physicists in the dosimetry calculations is shown in Fig. 10. For the majority of treatments, a medical physicist is always involved when dosimetry is performed.

Three-eight percent (38%) of centres indicated that they took part in clinical studies involving dosimetry in the past five years, with the majority of them (68%) performing the dosimetry at their own centre. In 42% of centres, dosimetry for clinical studies was performed at other centres (sometimes in addition to at their own centre). Centres that indicated they perform dosimetry, were asked what software is typically used for the calculations. More than 60% of the centres indicated they have in-house developed software available, and 46% of the centres had commercial software available (Fig. 11A). Eighteen percent of centres indicated they did not use any software to perform dosimetry calculations.

When asked how centres ensured the quality of their dosimetry calculations, the most common method was by quality assurance of the devices used (over 70%, Fig. 11B). Other methods included the use of verified software for dosimetry, the use of standard operating procedures (SOPs) and review of the results by a second person (all used in between 30% and 40% of centres). Seventeen percent (17%) of centres indicated they did not have a dedicated procedure in place to ensure quality of dosimetry calculations.

4. Discussion

The 173 analysed responses received from 27 different European countries showed that the majority of centres (84%) perform dosimetry for at least one treatment. The implementation varied widely between therapies, from almost all centres performing dosimetry-based planning for microsphere treatments to none for some of the less common treatments (like $^{32}$P sodium-phosphate and $^{89}$Sr$\text{SrCl}_2$). For treatments with less pronounced overall results, there was a large variation in practice between countries, and in some cases within countries. In general, this trend was noticeable in dosimetry for treatment planning as well as in post-therapy verification dosimetry.

The most common MRTs were Na$^{131}$I-based treatments and $^{223}$Ra$\text{RaCl}_2$. For each of these, over 100 centres responded they perform them annually (Fig. 3). The treatments performed and their respective frequencies were roughly similar between countries (Fig. 4). Direct comparisons with the frequencies found in a survey performed in 2015 are not straightforward [5], as the total numbers of treatments and patients were requested in the previous survey and categorical indicators were used in the current survey. However, since then there appears to have been a clear increase in the use of $^{177}$Lu$\text{Lu-PSMA}$, also supported by other publications [11–14], and potential increases in e.g.
Overall, 84% of responding centres reported to perform dosimetry for at least one type of treatment (Fig. 1). While this indicates that the expertise for performing dosimetry is currently present at most of centres, it should be mentioned that the extent of expertise needed for implementing dosimetry may vary widely for different treatments. Expanding dosimetry practice to other treatments should therefore always be preceded by considerations of resources and training implications. The role of the medical physicist is also evident, as only 2% of the centres reported performing dosimetry without physics support. For the majority of treatments, a physicist was always involved in dosimetry; only for a few treatments larger fractions responded that physicists were only involved during set-up (radiation synovectomies, [153Sm]Sm-EDTMP and [223Ra]RaCl2, Fig. 7). It should however be noted that the statistical foundation for these three treatments is very limited, with only 1–4 responses for each. The availability of physicists may be a limiting factor for the implementation of dosimetry, as most centres reported to have more than zero, but less than 0.5, FTE physicists involved in dosimetry calculations (Fig. 6). Nonetheless, there were differences between countries in this regard as well, with some centres having more than 3 FTEs. There were no obvious trends between the number of FTEs and the implementation of dosimetry on a country-level. While it would be interesting to explore this by statistical analyses, in a recent Italian survey conducted in 2019 [8], high numbers of pre- and post-therapy dosimetry were found in a recent Italian survey conducted in 2019 [8]. Dosimetry for the microsphere treatments can be performed with only one image acquisition, as only physical half-life needs to be considered. Over the
last years, recommendations from one of the vendors of microsphere radiopharmaceuticals have also evolved, with dosimetry now being preferred over the historical body-surface-area approach. This is likely also associated with the increase in centres performing dosimetry. At the other end of the scale are treatments such as $^{32}\text{P}$ sodium-phosphate, radiation synovectomies, $^{153}\text{Sm}$-EDTMP (Quadramet®), $^{223}\text{Ra}$ RaCl$_2$ (Xofigo®), $^{90}\text{Y}$-ibritumomab tiuxetan (Zevalin®), and $^{89}\text{Sr}$ SrCl$_2$, for which it is technically challenging to estimate dosimetric parameters. These are performed very rarely, and/or delivered as local therapy [15]. For these treatments, almost no dosimetry is performed. Treatments with the most varying results for dosimetry included the more recently introduced $^{177}\text{Lu}$-DOTATE and $^{177}\text{Lu}$-PSMA treatments. Both are based on fractionated regimens, and e.g. dosimetry-based planning may therefore be based on imaging performed after the

![Fig. 8. Overview of the use of dosimetry for treatment planning (left) and verification (right) for each treatment, at the country level. EU: Europe, here representing the overall results from all survey responses. Grey: no dosimetry is performed; light blue: dosimetry is sometimes performed; dark blue: dosimetry is always performed; no bars: treatment not reported performed in this country. The bars are normalised to the total number of centres performing the therapy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)](image)
first therapy fraction is delivered [16]. This may give rise to some interpretation variations for the questions “Does your centre perform this treatment dosimetry-guided? (e.g. activity adaptation, decision on treatment cycles, etc.)” and “Does your centre perform post-treatment dosimetry (i.e. for verification purposes)?”. For example, the response rate for dosimetry-guided treatment may be underestimated if responders interpreted this question to relate strictly to pre-treatment planning (i.e. performed before the first fraction is delivered). This may also contribute to a somewhat mixed trend compared to the 2015 numbers, when approximately 70% reported to never plan the absorbed dose for each patient and 30% reported to never perform post-therapy dosimetry for $^{177}$Lu-DOTATATE (compared to approximately 50% and 40% in the current survey, respectively). For $^{177}$Lu-PSMA the percentage of centres performing post-therapy dosimetry has decreased between surveys; from no centres answering ‘Never’ in 2015, to just above 40% now. This is probably a result of more and more centres moving from performing this treatment in a research setting only, to using it in routine settings, and adhering to the fixed posology approved by the manufacturer [17]. Also for Na$^{131}$I treatments certain variations in dosimetry implementation were observed between centres, although comparisons with 2015 numbers indicate an overall relatively stable situation. Less than 40% of responders reported to perform dosimetry-based treatment planning for $^{131}$I-meta-iodobenzylguanidine ($^{131}$I-mIBG) therapy for neuroblastoma in children, showing little change from 2015 (around 35%). Here, some of the more pronounced inter-country variations were observed, with national harmonised practice within most countries. The lack of progress for $^{131}$I-mIBG is somewhat disappointing; especially since a guidance document published in 2020 described a whole body approach requiring limited time and equipment [18]. This is a paediatric patient group for which
dosimetry is particularly relevant and finding a common best practice should be prioritised in the future. Investigations of the underlying reasons for discrepancies were outside the scope of the current survey, however, different transpositions of the EURATOM directive in national legislations, resource limitations, and lack of established dose–effect correlations for some treatments may be among the factors.

Whether dosimetry was performed mainly for normal tissues at risk or regions of disease, varied widely per treatment (Fig. 9A). For most treatments, both tissue types were of interest. For Na\[^{131}\mathrm{I}\] treatments of benign thyroid disease, the focus was mostly on regions of disease, probably because for these treatments, the therapeutic window is very wide, making the normal tissue complication probability low for the relevant activities [19]. This was also found for radiation synovectomies, which are delivered in a highly localised manner, minimising the need for normal tissue surveillance. Accordingly, no responders reported to perform dosimetry for normal tissues for these treatments.

Responders were asked if they use commercial or in-house software for dosimetry, and interestingly 18% of centres indicated to use no software at all (Fig. 11A). However, this might be the result of interpretation of the term software (e.g. the use of Excel could be interpreted as both commercial software, as in-house developed software if a specific Excel file was created for the calculations, or it might be interpreted as no software since this is no specific dosimetry software). The results from this question should therefore be interpreted with care. Of the centres performing dosimetry, the majority had at least one procedure in place for quality assurance of the dosimetry; ensuring QA of devices being the most frequently implemented (Fig. 11B). Around 17% of centres indicated to have no QA procedure in place, including not using verified software for dosimetry. However, half of these centres indicated in the previous question that they use commercial software for dosimetry and this may again be related to the interpretation of ‘software’. It must be mentioned that ensuring QA of devices, which is also considered a crucial step, mainly ensures the quality of the input data and not the dosimetric approach itself. It is therefore open to discussion whether this is actually QA of the dosimetry per se: if not, the percentage of centres without a QA procedure in place would approximately double (responders with “No procedure” and solely “Ensuring QA of devices”).

The initial survey was conducted between April and June 2022. Due to a methodological error in the online survey form, part of the responders did not receive all questions initially. For this group, a follow-up survey was set out between July and September 2022. Only responders that had completed this second part of the survey (if applicable) were included for analysis, leading to the exclusion of 22 responses (Fig. 1). Due to the same error, only 113 of 146 responses performing dosimetry could be analysed for questions on dosimetry software and quality assurance. Also, the initial survey included a question on the use of pre-clinical dosimetry. When analysing the results it became clear that many centres interpreted this as ‘pre-treatment’ instead of ‘not-human’. As a result it was decided to omit this question from the analysis. Lastly, it is important to mention that the results of this survey reflect the situation in 2022, and the implementation is expected to continue to develop in the near future.

5. Conclusion

Similarly to what was found in earlier surveys, there is a wide variation in the use of MRT both across and within countries. Implementation of dosimetry, both for pre-therapeutic treatment planning and post-therapy absorbed dose verification, has increased for several treatments, especially for microsphere treatments. For other treatments that have moved from research to clinical routine, the relative use of dosimetry decreased in recent years. When dosimetry is performed, a medical physicist is almost always involved at some level, and some form of quality assurance is commonly implemented. Further increase in applications of MRT, and implementation of the Council Directive 2013/59/Euratom and corresponding position papers might lead to adaptations in the use of radionuclide dosimetry in the near future. Therefore, a regular update of the survey results is recommended to follow the development of dosimetry across Europe and to ensure the alignment and standardisation of dosimetry for MRT.

Declaration of competing interest

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Appendix A. Supplementary data

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