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Implementation of dosimetry in molecularradiotherapy in Spain. Results from a Spanish survey

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ABSTRACT

Introduction: The implementation of the dosimetry and optimization requirements for radiopharmaceuticals of therapy, established in the Euratom Safety Standards Directive (EC Directive 2013/59/Euratom), is a major challenge in European countries. The aim of this study is to evaluate the current practice in molecular radiotherapy (MRT) in Spain.

Methods: An electronic questionnaire has been distributed to Spanish Nuclear Medicine Departments (NMDs) in order to have an overview of the current situation with regard to the optimization of radiopharmaceutical therapies and the analysis of the resources available in hospitals.

Results: This survey received 24 replies, which represents 16 % of the total number of Spanish NMDs geographically distributed over 17 Spanish Autonomous communities.

A Quality Assurance Program (QAP) has been developed in 96 % of Spanish NMDs that replied to the survey, and 86 % of these QAPs include the criteria for justifying medical exposure. Regarding staff knowledge of the provisions of Directive 2013/59/Euratom, 70 % of the responses were positive. A high level of compliance with the Summary of Product Characteristics for each therapy was observed in relation to the officially approved conditions of use of radiopharmaceutical therapies.

Planning of the activity to administer with physician involvement is used only for non-standardized procedures (70 %). However, non-standardized procedures do not seem to be common practice. The use of activities based on fixed-activity protocols is more than 82 % for all therapies, except for the radiopharmaceutical I-131 MIBG (56 %). As regards the assessment of the resources available to carry out dosimetry-guided treatments, only 4 % considered them to be adequate.

Conclusion: Patient-specific dosimetry has not yet been implemented in Spanish NMDs as a daily routine due to the lack of resources, training and specific regulatory instructions to perform it.

1. Introduction

Molecular radiotherapy (MRT) is an evolving field in cancer treatment that involves administering radiopharmaceuticals to target and treat malignant tissues (Davis et al., 2023; Gustafsson and Taprogge, 2023). The implementation of dosimetry in MRT is crucial for optimizing treatment efficacy and minimizing side effects.

It is essential to emphasize that radiopharmaceuticals (RPs) are classified as both medicinal products and radioactive substances; therefore, two directives govern their regulation within the European Union. Directive 2001/83/EC (European-Council, 1989), which covers the pharmaceutical aspects, and Directive 2013/59/Euratom (European-Council, 2014), which covers the basic safety standards for protection against the dangers arising from exposure to ionizing radiation. In this context, the preparation of radiopharmaceuticals involves

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List of abbreviations:

AEMPS	Spanish Agency for Medicines and Medical Devices
BSSD	Euratom Safety Standard Directive
EANM	European Association of Nuclear Medicine
Er	Erbium
GMPs	Good Manufacturing Practices
MIBG	Meta-iodobenzylguanidine
MSC	Spanish Ministry of Health
MRT	Molecular Radiotherapy
NMDs	Nuclear Medicine Departments
QAP	Quality Assurance Program
Re	Renium
SEMNIM	Spanish Society of Nuclear Medicine and Molecular Imaging
SmPC	Summary of Products Characteristics
UCM	Complutense University of Madrid
UE	European Union
Y	Yttrium

compliance with radiation protection regulations. The dosimetry and safety of radiopharmaceuticals in non-industrial manufacturing and clinical use are critical for optimizing patient outcomes and ensuring safety for healthcare providers. Recent advancements in internal dosimetry are enhancing personalized treatment approaches, while regulatory frameworks are guiding safe practice (European-Commision, 2006; Lassmann et al., 2021; O'Donoghue et al., 2022).

The use of radiopharmaceuticals for therapy has increased in recent years, with a significant number of molecular radiotherapies now authorized in Europe and others in the late stages of clinical trials (Lassmann et al., 2021). However, when the Pharmaceuticals Directive (European-Council, 1989) was adopted, most radiopharmaceuticals were used for diagnostic purposes, and the amendments made to the Directive did not take into account the progress in the use of molecular radiotherapies.

The dosimetry and optimization requirements are established under the Euroatom Safety Standard Directive (BSSD), EC Directive 2013/59/Euratom (European-Council, 2014). In its article 56 is stated *that "exposures of target volumes in nuclear medicine treatments shall be individually planned and their delivery appropriately verified"*. In the Pharmaceuticals Directive, the specific requirements of the BSSD to optimize treatment with ionizing radiation are reflected in article 4 and Article 11. It was also mentioned in the previous version of European Medicines Agency Guideline of Radiopharmaceuticals 3AQ20a (EMA, 2008). However, their application in daily practice still seems to be limited, as there may be discrepancies between the activities to be administered as indicated in the Summary Product Characteristics (SmPC) and the activities individually planned according to dosimetry (Chiesa et al., 2017).

Spain transposed Directive 2013/59/Euratom into its national regulatory framework by Royal Legislative Decree 601/2019 (MSCBS, 2019). In addition, Royal Decree 673/2023 (MS, 2023) on quality and safety criteria for nuclear medicine care units was published. The latter mentions the optimization of MRT doses. However, the implementation of Article 56 of Directive 2013/59/Euratom (European-Council, 2014) does not seem to be sufficiently developed to provide Spanish NMDs with the necessary tools and resources for an adequate implementation of dosimetry practices to comply with the BSSD. This issue is of great concern to the Spanish Ministry of Health (MSC), in line with the rest of the European Union (UE) regulatory bodies. For this reason, the UE countries are collaborating in European Commission projects, such as SIMPLERAD, to improve the understanding of the links and interdependencies between European pharmaceutical legislation and Euratom radiation protection.

The European Association of Nuclear Medicine (EANM) is also collaborating with the SIMPLERAD project to promote the coherent implementation of European regulatory requirements for therapeutic nuclear medicine. In this context, the EAMN launched a European survey in 2016, which revealed a wide variation in therapeutic practice among European centres (MS, 2023).

As the Directive should have been implemented in Spain in 2018, in order to try to have an objective and global view of the practice, a survey has been conducted to define a clear picture of the usual practice in the use of RPT and the potential variability between the various Spanish NMDs.

2. Materials and methods

2.1. General

"An electronic questionnaire has been distributed to Spanish NMDs in order to have an overview of the current situation with regard to the optimization of radiopharmaceutical therapies and the analysis of the resources available in hospitals."

This is an electronic questionnaire, part of a joint project between the Faculty of Pharmacy of the Complutense University of Madrid (UCM) and the Spanish Agency for Medicines and Medical Devices (AEMPS).

Spanish Society of Nuclear Medicine and Molecular Imaging (SEMNIM) launched the survey as a newsletter in June 14, 2023. In July 2023, kind reminders were sent individually to the head of services and a new newsletter has been distributed by SEMNIM. The survey was closed on July 15, 2023.

2.2. Survey structure

The electronic questionnaire has an introductory page explaining the purpose of the survey and is divided into three parts:

- The first part contains general questions about a quality assurance program and the implementation of basic safety standards, as well as questions about the involvement of **medical physics expert**. Finally, an assessment of the resources available to perform patient-specific dosimetry.
- The second part was designed as a therapy page. There were 9 therapies explicitly considered, as listed in Table 1. All of these are licensed therapies with licensed and commercially available radiopharmaceuticals included in ATC code V10. Medical devices were not included in this survey.
- The last part was a space for free text comment.

2.3. Data analysis

Microsoft Forms was used to create the electronic questionnaire. The statistical, descriptive and inferential analysis has been carried out with the IBM SPSS package (v 29.0.) In addition, a contingency analysis was performed considering the classification of type 2 (less than 500 beds) versus type 3 and 4 (more than 500 beds) hospitals to analyze whether there was a significant difference using the software GraphPad Prism v8.0.

The survey was written in Spanish and implemented as a web-based questionnaire. All records in the web database were exported to a file and manually curated. This process included removing inconsistent data and merging records.

3. Results

The original newsletter sent to the Heads of Nuclear Medicine Departments (NMDs) was opened by a 44.1 % and the link to the survey was clicked by 26.1 %. The total number of respondents was 24, geographically distributed over 17 Spanish Autonomous communities.

Table 1
Therapy types included in the survey.

Annotation	Radiopharmaceutical	Indication
A	***Iodine-131***	*Non-oncological indications: Hyperthyroidism; Treatment of Graves' disease toxic multinodular goitre or autonomous nodules.*
B	***Iodine-131***	*Oncological indications: Treatment of papillary and follicular thyroid carcinoma including metastatic disease.*
C	***Lutetium (177Lu) oxodotreotide (Luthatera®)***	*Unresectable or metastatic, progressive, well-differentiated (G1 and G2), somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults.*
D	***Radium 223 dichloride (Xofigo®)***	*Treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.*
E	***I-131 MIBG***	*Pheochromocytomas, neuroblastomas, carcinoid tumors, and medullary thyroid carcinomas.*
F	***153Sm-EDTMP (Quadramet®)***	*For bone metastasis*
G	***90Y-, 186Re-, or 169Er-colloids***	*Radiation synovectomy*

3.1. General questions

In this general section, the first question refers to the classification of hospitals according to the number of beds; thus, 8 % of NMDs were located in type 2 hospitals (200–500 beds), 52 % in type 3 (501–1000 beds) and 13 % in type 4 (more than 1000 beds). The contingency analysis carried out, taking into account the classification of type 2 versus type 3/4 hospitals, did not show significant differences, ruling out an involvement of the hospital size in any of the items analyzed. However, the sample size was limited to 24 and larger studies could be needed to explore subtler differences. In fact, the 65 % of the NMDs included in the survey has a radiopharmacy unit with no differences between type 2 and type 3/4 hospitals.

Concerning the Quality Assurance Program (QAP), two questions were formulated. The first one was about the availability of a QAP and for those answering affirmatively, a second one was posed regarding inclusion of criteria for justifying medical exposure in the QAP. A 96 % of the NMDs confirmed to have a QAP and only a 14 % of the QAP did not include the criteria for justifying medical exposures. 39 % of the NMDs confirmed to have a dosimetry calculation program (Fig. 1).

For these general questions, the results displayed in Fig. 2 show that dose planning was always performed in 13 % of cases. It was never performed in 17 % of cases, and non-standard procedures were always performed in 70 % of cases. The SmPC was always checked in 78 % of cases, and the medical physicist was always involved in 35 % of cases.

3.2. Assessment of available resources

In response to the general question "*How would you rate the current resources available for implementing patient-specific dosimetry in your hospital*?" four responses were possible: very poor, poor, acceptable and adequate. The mean frequencies for all NMDs were very poor (35 %), poor (43 %), acceptable (17 %) and adequate (4 %).

3.3. Available therapies

In this part of the survey, nine therapies explicitly were considered, as listed in Table 1.

Concerning to the first question asked for each therapy "*How often is a fixed-activity protocol used?*", results are displayed by combining all data into two main categories, "Always/Majority" and "Minority/Never". As it is shown in Fig. 3, for all therapies, the percentage for always/majority is above 82 % with the exception of the radiopharmaceutical I-131 MIBG with a percentage for 56 %.

For the question "*Is the medical physicist involved in the treatment?*" only one answer can be replied, consisting of Always, Majority, Minority or Never. As it can be seen in Fig. 4, for all therapies, the answer "never" was over 50 % and in some cases (I-131) as high as 92 %. The responses given in this question are in line with the following question "*Is the absorbed dose individually planed?*". The answer "never" was over 70 % in

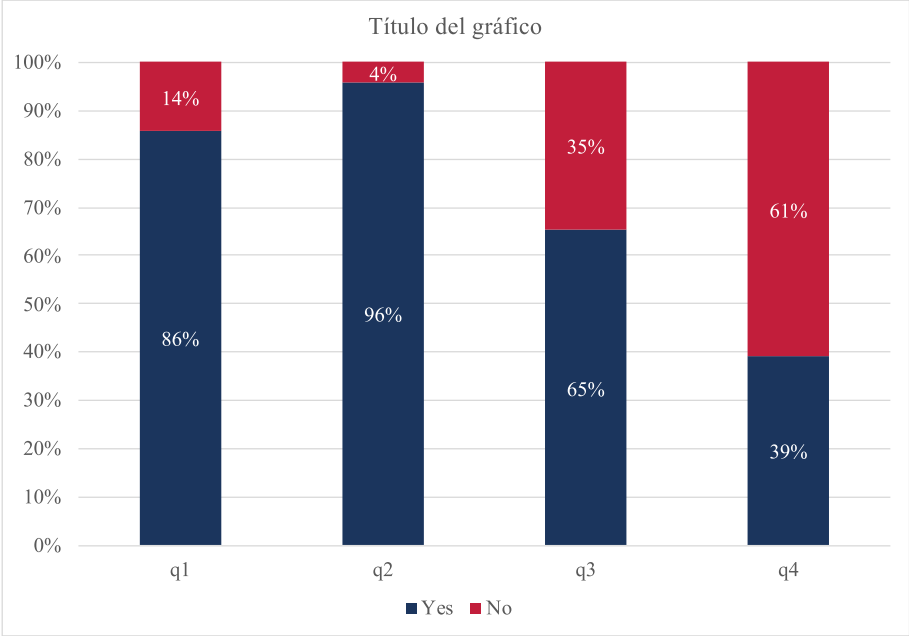

Fig. 1. Replies to general questions (%):q1:Are included dose optimization and justification in QAP?"; q2: Is there a quality assurance program in place? q3: Does your Nuclear Medicine Department have a Radiopharmacy unit?"; q4: Does your department have a dosimetry calculation program? "

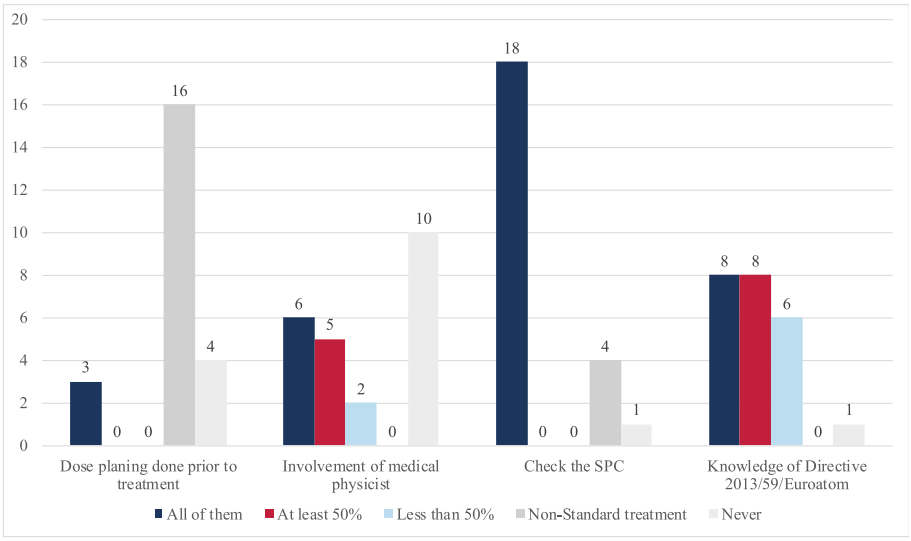

Fig. 2. Replies for the following questions: q5: "Is estimated dose planning done prior to treatment? "; q6: "Is the medical physician involved in each treatment?; q7." Is the SmPC checked before the RPT administration?" q8:"Are the staff of your Nuclear Medicine Department aware of the provisions of Directive 2013/59/Euratom, Article 56 on the planning of radiation doses administered to individual patients?"

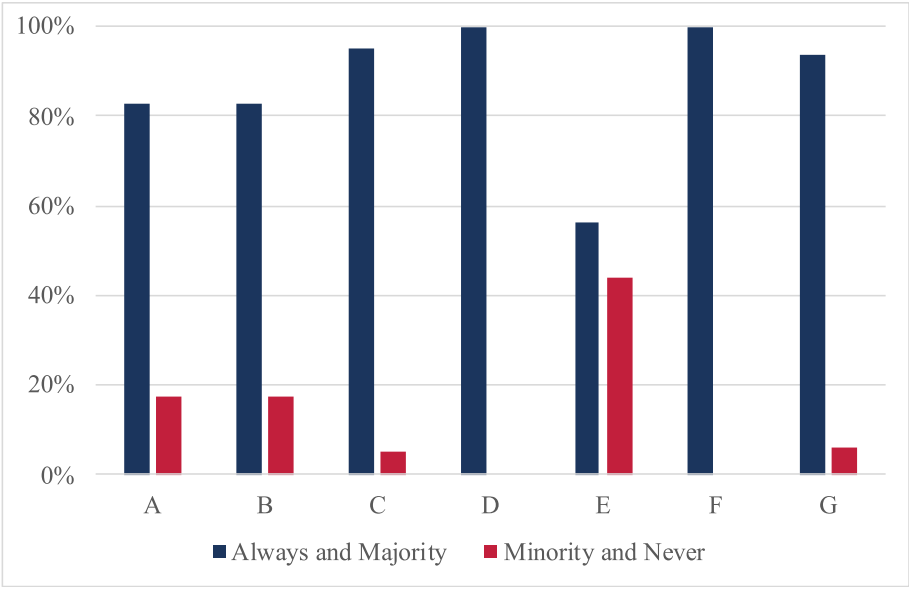

Fig. 3. Replies (%) for question" How often is a fixed-activity protocol used?", numbers of the vertical axis represent the percentage of the total number of responses analyzed combining the data into two categories, namely Always/Majority versus Minority/Never.

all therapies, with the exception of I-131 MIBG (31 %) (Fig. 5).

Concerning the question "*Is the post-therapy dosimetry performed?*", the answer "never" was over 55 % for all the therapies (Fig. 6). Regarding the dosimetry in the critical organ, defined as the part of the body most vulnerable to a given isotope (MS, 2023), Fig. 7 shows that, with the exception of Luthatera (53 %), the critical organ was never taken into account in more than a 64 %.

3.3.1. Compliance with summary of Products Characteristics (SmPC)

The degree of compliance with the SmPC was assessed for each therapy in relation to the officially approved conditions of use of RPTs. Overall, preliminary results show a high degree of compliance with the SmPC, for example, overexpression of the somatostatin receptor in tumour tissue was always confirmed, as was the case with the use of Luthatera. Similarly, an infusion of amino acid solution was always given to protect the kidneys. In addition, laboratory tests to assess the patient's condition were confirmed in 100 % of treatments and, in the case of I-131 MIBG thyroid blockade was confirmed in 94 % of treatments.

3.3.2. Free-text comments from the responders

A free text field was available to collect additional comments from participants. Comments were coded in five classes (see Fig. 8).:

- Resources available for performing dosimetry (code:**RD**)
- Fixed activity protocols and SmPC (code:**FAS**)
- Microspheres and radioembolization (code **MR**)
- Role of the physician and medical physicist (code: **PP**)
- Other (code: **OT**).

Figure eight shows that 27 % of the comments related to the lack of resources available to perform dosimetry studies. The 36 % of comments

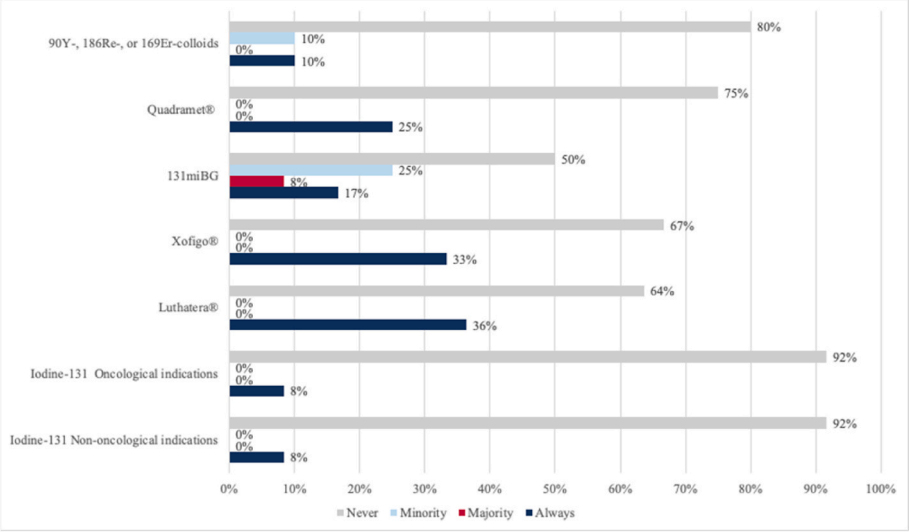

Fig. 4. Replies (%) for question "Is the medical physicist involved in the treatment".

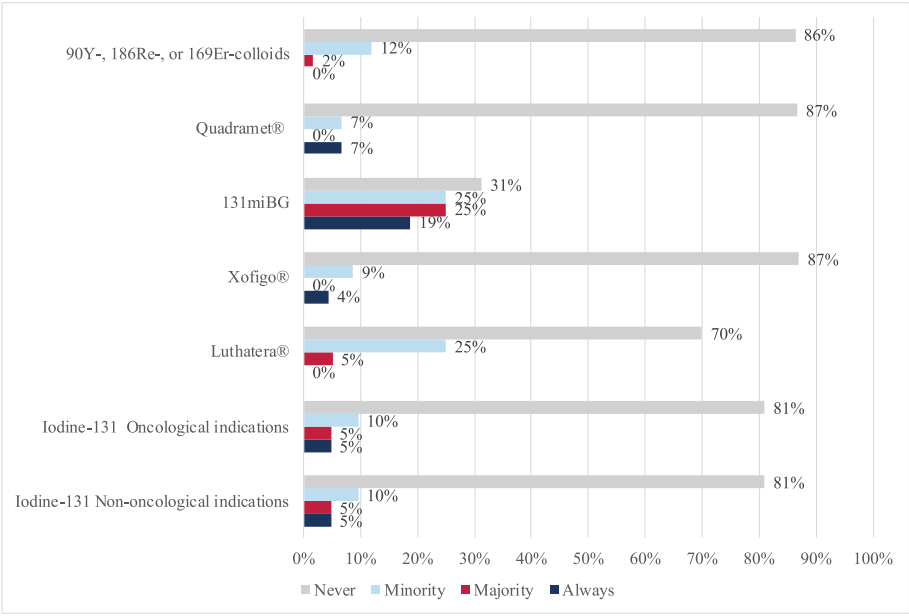

Fig. 5. Replies (%) for question" "Is the absorbed dose individually planed.?

related to the activity - fixed protocols and compliance with the SmPC. In particular, two of the respondents pointed out that patient-specific dosimetry should only be introduced for new therapies, as the risk-benefit balance is well known for established therapies. Otherwise, its introduction could reduce the quality of medical care.

18 % of respondents said that some of the treatments included in the survey had been replaced by more effective ones and that microsphere therapies had not been included.

9.9 % of respondents stated that the responsibility for non-compliance with the SmPC should lie solely with the physician.

4. Discussion

This is the first survey focused on implementing personalized dosimetry in Spain. As with all surveys, depending on the number of participants, the results might be scaled to be representative of general practice. This survey received 24 replies, which represents 16 % of the total number of NMDs according to the data given on the SEMNIM website (150 NMDs in Spain). This result is comparable to the European survey launched in 2016 (Sjögreen Gleisner et al., 2017), where the 208 respondents were estimated to represent around 20 % of existing centres. We consider this to be an adequate number, given that the responses were anonymous, which increases the credibility of the results. Thus, it provides a clear picture of the current situation of Spanish NMDs and it could be a starting point for the implementation of dosimetry.

4.1. General questions

With regard to the responses to the general part of the survey, it is noteworthy that 94 % of NMDs have developed a Quality Assurance Program (QAP). 86 % of these QAPs include the criteria for justifying medical exposure. These results, together with the 70 % of positive responses regarding staff knowledge of the provisions of Directive 2013/59/Euratom, show that the implementation of dosimetry practice to comply with the BSDD is a major concern in Spanish NMDs.

However, planning of the activity to administer with physician

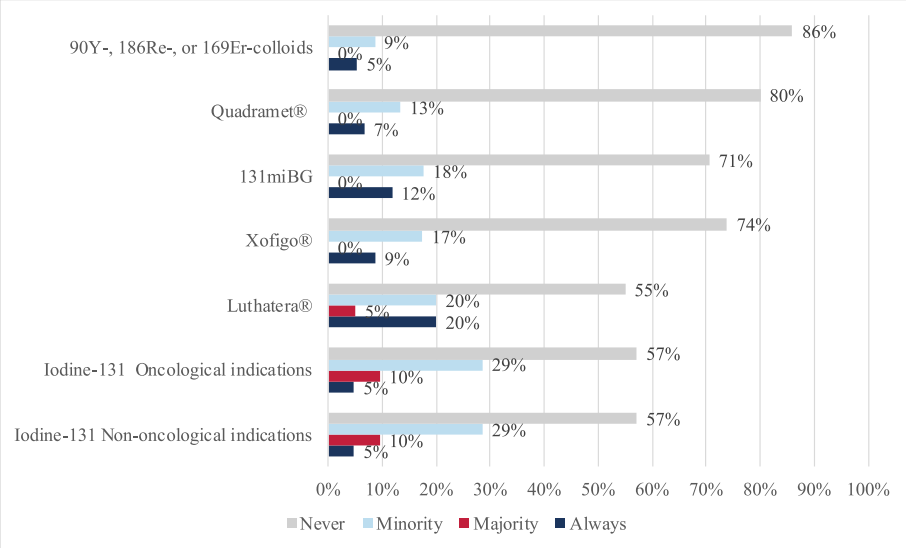

Fig. 6. Replies (%) for question "Is post-therapy dosimetry performed?"

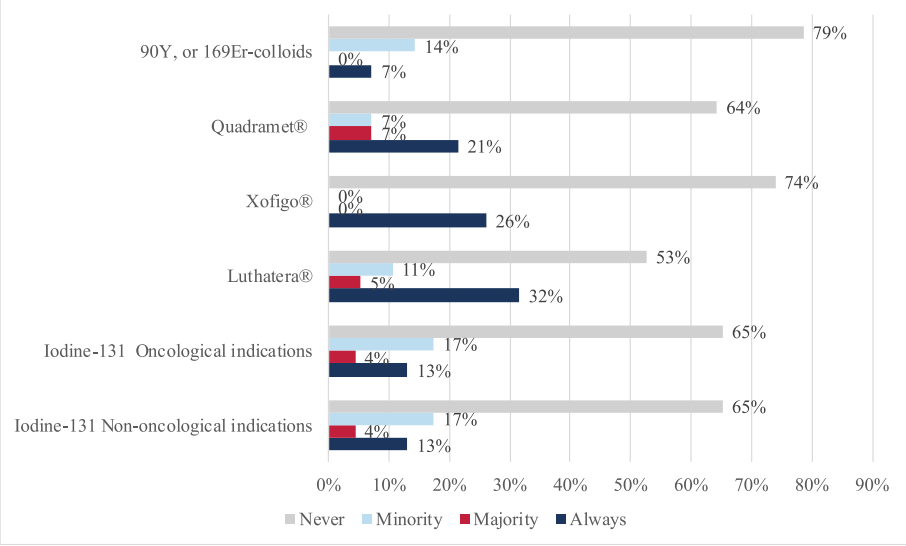

Fig. 7. Replies (%) for question "Is the dosimetry of critical organ taken into account?".

involvement is performed only in non-standard procedures (70 %), but non-standard procedures do not seem to be common practice, as the percentage of Summary Product Characteristics (SmPC) review is 78 %. This is in line with the assessment of availability of patient-specific dosimetry resources (very poor (35 %) and poor (43 %)).

4.2. Therapies

In relation to the activities to be administered, it is worth noting the use of activities based on fixed-activity protocols for all therapies (more than 82 %), except for the radiopharmaceutical I-131MIBG, which accounted for 56 %. This decrease in the percentage of I-131MIBG is to be expected, as its SmPC specifies that the posology should be adapted on an individual basis after a dosimetry study, whereas dosimetry is not specified in the SmPC of the other therapies. These results are in line with the observed high level of compliance with the SmPC in Spanish NMDs.

The results obtained with regard to dose planning and the involvement of the medical physicist are consistent with the data presented above. Thus, the "never" response was greater than 70 % and 64 % respectively for all therapies except I-131MIBG. Similarly, post-therapy dosimetry was never performed in more than 55 % of cases and critical organ dosimetry was not considered in more than 53 % of cases.

4.3. Free comments from responders

This section reflects the fact that daily practice in nuclear medicine services is based on fixed-activity protocols according to the SmPC. Resources for the implementation of patient-specific dosimetry are not currently available.

4.4. Summary

As a summary, the Spanish survey showed that the implementation of patient-specific dosimetry could be a major concern for nuclear medicine services in Spain, as reflected in their quality assurance programs. Even though the BSSD have been incorporated into our national legislation since 2019 with Legislative Decree 601/2019 (MSCBS, 2019), the practice of dosimetry has not yet been implemented as a daily routine. It seems that a new regulatory approach with clear instructions

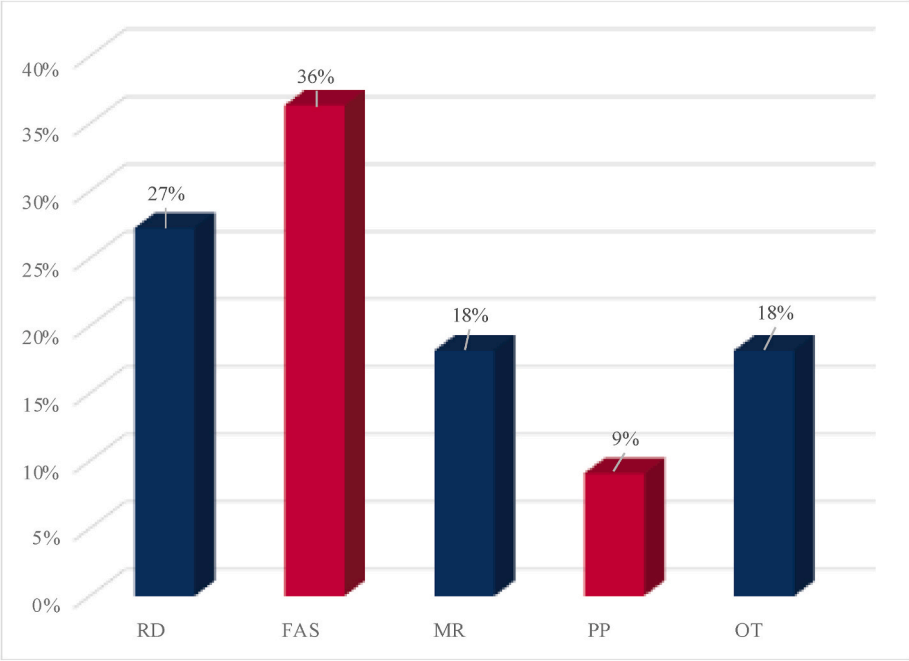

Fig. 8. Free comments quantification. RD: Resources Dosimetry; FAS: Fixed-Activities- SmPC MR = Microsferes and Radioembolization; PP: Physician and Medical physicist; OT:Others.

would be necessary to ensure the correct implementation of this practice. In this way, a similar approach is being taken by other European countries, such as Italy, where a position paper with recommendations for the optimization of dosimetry in nuclear medicine therapy has been published (Chiesa et al., 2021).

In the UK they have released also a position paper agreed between the nuclear medicine and the medical physics national societies (Flux and Buscombe, 2021). The European Federation of Organisations for Medical Physics (EFOMP) also presents a number of recommendations to support the transition from administrations of fixed activities to personalized treatments based on patient-specific-dosimetry (Sjögreen-Gleisner et al., 2023).

Similarly, the EANM has also published a position paper to provide guidance on how to interpret the statements of the Directive for nuclear medicine treatments (Konijnenberg et al., 2021).

However, although European countries are working together (SIMPLERAD project) to promote the implementation of European regulatory requirements for therapeutic nuclear medicine, and relevant general and specific guidelines have been published by the EANM Dosimetry Committee (Chiesa et al., 2021; Gear et al., 2018, 2020; Sjögreen Gleisner et al., 2022), there are still potential barriers to the coherent implementation of dosimetry requirements.

The resources available to optimize RP therapy doses are insufficient, as reflected in previous survey results. For example, there may be instrumental limitations to obtaining an accurate dosimetry assessment. There are also logistical barriers, such as the impossibility of repeating scans for some patients and the availability of cameras in the Spanish NMDs.

Another important limitation is the lack of adequately trained medical physicists. In contrast to external beam radiotherapy, in nuclear medicine therapy there are situations where the absorbed dose to the target volume cannot be calculated or reliably predicted for technical or practical reasons (Chiesa et al., 2017). Additionally, radiobiology would be necessary to improve estimation and prediction of efficacy and adverse effects (Aerts et al., 2021). For this reason, an adequate training would be necessary in this field (Flux et al., 2018). In Spain, there is an official specialty for hospital medical physicists and the educational requirements to obtain this specialization are 3 years of practical experience in a university hospital (MPR, 2008). However, the training program should have been updated to include, among other subjects, more specific training in dosimetry and radiobiology for the implementation of BSSD.

Even if all the barriers described above (resources, logistics, training, etc.) could be overcome and dosimetry could be implemented, there would still be another important issue to be addressed: the insufficient link between EU pharmaceutical legislation and BSSD. Most of these RPTs have been evaluated through the centralized procedure of the European Medicines Agency (European-Council, 2004). The EMA's assessment is based on a balance of benefits and risks, and for each radiopharmaceutical, a posology to be followed is approved by its SmPC (European-Commision, 2009). However, in order to comply in Spain with the requirement for optimization as set out in the BSSD, it would be necessary to apply Royal Decree 1015/2009 of 19 June 2009 (MSPS, 2009). This Royal Decree regulates the availability of medicinal products in special situations (off-label use), which would lead to confusion as to which Directive should prevail in the absence of guidance from the EU authorities on the implementation of the BSSD.

For this reason, dosimetry should be performed in initial clinical trials to provide relevant information for the use of RPT (Stokke et al., 2024). Clinical trials are now centrally evaluated through the Clinical Trials Information System due to the new Clinical Trials Regulation (EU) No 536/2014, (European-Council, 2022) which came into force on 31 January 2022. Although this regulation includes in its Questions and Replies (Q&A) information on how sponsors are expected to justify radiation exposure in clinical trials, it seems that it is not being yet implemented.

5. Conclusions

The personalization of dosimetry with radiopharmaceuticals of therapy is considered a major concern for Spanish NMDs and is included in their national regulation. However, patient-specific dosimetry has not yet been implemented as a daily routine due to the lack of resources, training and specific regulatory instructions to perform it.

It seems that much remains to be done to achieve the implementation of dosimetry-based treatment planning and the verification of absorbed

doses delivered after administrations, as it will require a major reassessment of how these treatments are conventionally delivered.

CRediT authorship contribution statement

Estrella Moya: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Celia Cerrato:** Writing – review & editing, Supervision. **Luis Miguel Bedoya:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Jose Antonio Guerra:** Writing – review & editing, Visualization, Supervision, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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