



Original Article

Building an appraisal framework for radiotherapy innovations in a value-based context: The ESTRO-Value-based radiation oncology categorisation system

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ABSTRACT

Aim: There is no consistent appraisal strategy for radiotherapy innovations supporting their clinical implementation or regulatory decision-making, thus hampering access to high-value care. This study presents the development of a categorisation system as a first step towards a value-based appraisal framework for radiotherapy innovations within the ESTRO Value-Based Radiation Oncology (VBRO) project.

Methods: A mixed-method development process in four phases integrated qualitative and quantitative data in multiple rounds of revision, improvement and validation; and was supported by multidisciplinary stakeholders representing the European radiation oncology community.

Results: Four distinct categories of radiotherapy interventions are defined: Drug-centred, Radiation-centred, Radiation-enabling and Operational radiation interventions. Innovations are categorised based on their primary aim, focussing on either patient-level or organisational level; their technological characteristics; and their radiotherapy-specific characteristics such as therapeutic ratio, biological or dosimetric properties or radiotherapy-drug combinations. To support categorisation choices, a sequence of decision-making questions was arranged in a decision algorithm and presented as a decision tree. The categories and categorisation algorithm were validated using qualitative and quantitative methods by representative stakeholders of the European radiation oncology community, by a bibliometrical data analysis, and finally by the VBRO steering committee.

Conclusion: A correct definition of the different radiotherapy categories is essential to study their interrelation with optimum study design, outcomes, and magnitude of benefit, in view of optimising evidence generation and tailored appraisals. This categorisation system forms the basis to create a value-based appraisal framework within the ESTRO-VBRO project, aimed to support implementation and authorisation regulations for each category of radiotherapy innovation.

Introduction

Radiation oncology is a fundamental component of cancer management, with the demand expected to increase both in volume and in

complexity due to evolving demographics, changing treatment patterns and the rapid introduction of innovative interventions and technology advancements. [1–3] However, current evidence-based demand for radiotherapy is not adequately met, leading to a significant gap between

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the optimal and actual utilisation of radiotherapy, especially in low- and middle-income but likewise in high-income countries. [1,3,4]

Appraising radiotherapy innovations faces specific challenges that complicate robust evidence generation on meaningful endpoints as well as cost calculations, thereby contributing to this gap. [5] The heterogeneity of interventions, ranging from complex equipment (e.g. linear accelerators) to radiation beams with different biological properties (e.g. proton therapy), over novel fractionation schemes or innovative combinations with new cancer drugs, up to immobilisation and positioning strategies (e.g. masks), complicate standardised evaluation, resulting in variable levels of evidence in research output. [6,7] Additionally, many radiotherapy interventions primarily aim to improve local tumour control and/or reduce normal tissue damage, referred to as the therapeutic ratio. [8,9] These outcomes often take considerable time to translate into improvement of endpoints typically required to support clinical implementation or reimbursement, such as overall survival or quality of life. [10–12] High upfront investments, logistical demands and the need for advanced operator expertise can further complicate or delay evidence generation. [6,13]

The resulting lack of high-quality evidence on outcomes or costs for radiotherapy innovations hinders transparent evaluation, resulting in substandard care or inequitable access, or conversely, additionally straining healthcare budgets by adoption without sufficient evidence of benefit. [5,7,14–19].

The Health Economics in Radiation Oncology program of the European Society for Radiotherapy and Oncology (ESTRO-HERO) engaged to build a comprehensive framework using the concept of value in the Value-Based Radiation Oncology project (VBRO),² addressing the need for structured appraisal to support implementation and policy decision making. Value, defined as achieving health outcomes that matter most to patients per money spent across the entire care cycle, was introduced over a decade ago and has been adopted into frameworks to appraise systemic cancer treatments, such as the Magnitude of Clinical Benefit Scale by the European Society for Medical Oncology; the American Society of Clinical Oncology Value Framework; or the National Comprehensive Cancer Network evidence blocks™. [6,10,12,13,16,20] However, these existing frameworks do not account for radiotherapy-specific challenges, such as the diversity in radiotherapy innovations, the variability in level of evidence and the use of non-traditional endpoints, rendering the appraisal of benefit in radiotherapy less straightforward. [6,21]

Different types of interventions may entail different outcomes or require a different approach to evidence generation and study design, yet there is currently no widely accepted system to categorise radiotherapy innovations in view of their appraisal. [16,22] The present study outlines a multi-method approach undertaken within the ESTRO-VBRO project to develop such a categorisation system, tailored for value-based appraisal of innovative radiotherapy interventions in order to provide the required evidence for clinical implementation and healthcare policy decision-making. [6,16]

Methodology

A categorisation system for radiotherapy interventions was developed, based on an established multi-method approach by Jabareen et al. to develop integrative frameworks. [23] Multiple methodologies and data sources are combined iteratively in different phases to select and analyse relevant data, identify and deconstruct concepts to be integrated into a new framework, which then is finalised in multiple rounds of (re)

synthesis and validation.

Building on this approach, four phases were outlined. An overview of methods, stakeholders, and results for each phase is shown in Table 1 and visualised in Fig. 1.

A multidisciplinary group (AA, JB, MA, ML, MV, PB, YL), including backgrounds in radiation and medical oncology, medical physics, radiation therapy (RTT), epidemiology, health services research and policy, was defined as the steering committee. Involvement of the broader European radiation oncology community was ensured through the ESTRO, with input from additional experts for final validation.

Phase 1: Identifying and analysing existing categorisation systems.

As a first step, categorisation systems with potential application to radiotherapy innovations were identified through a systemic literature search. [22] Four radiotherapy-specific categorisation systems were found and critically appraised in relation to radiotherapy-specific characteristics used to categorise interventions, such as mode of delivery, radiobiological properties or type of equipment. A list of 23 radiotherapy interventions (Table 2) was created, using literature and expert input, to represent the diversity across radiotherapy interventions. In an iterative process, the steering committee categorised these interventions in the four available categorisation systems, to identify possible gaps in existing frameworks, and to define additional key elements for meaningful categorisation.

Phase 2: Defining meaningful categories.

The results of Phase 1 supported an in-person co-creation workshop aimed at defining different categories of radiotherapy innovations. The 23 interventions were used to test and approve a series of decision-making questions, assisting the categorisation of radiotherapy interventions and integrating the previously identified essential and radiotherapy-specific characteristics.

Each resulting category represents a group of distinct interventions, that aim to achieve particular outcomes (clinical and/or non-clinical), and that are expected to require a similar approach towards evidence generation and appraisal with regards to clinical implementation and healthcare policy decision-making.

Phase 3: Adapting and synthesising the categories into a decision algorithm.

The defined categories from the co-creation workshop were further refined in multiple rounds of discussion and categorisation exercises, in which the steering committee was asked to support its rationale for allocation of the 23 interventions into a particular category. Quantitative analysis of allocation choice and thematic analysis of the reasons given were discussed, and used to adjust the categories (definitions, inclusion criteria as well as consideration for new categories).

In addition, a decision algorithm was created by arranging the decision-making questions in the form of a graphical decision tree, to support the classification choices. The aim is that by following this decision tree, any intervention can be classified into the final list of categories following a logical stepwise process.

Discrepancies in wording or interpretation of the categories or the categorisation decision tree were resolved by consensus within the steering committee (minimum 5/6 consensus).

Phase 4: Validating the categories and categorisation system.

Qualitative and quantitative evaluation by representative stakeholders of the European radiation oncology community

Validation of the categories and the categorisation decision system was performed by the European radiation oncology community using a purposive sampling methodology. The eight ESTRO committees (Clinical, Physics, Biology, RTT, GEC-ESTRO, Young, National Societies and Radiation Oncology Safety and Quality Committees) were invited to delegate two to three representative committee members to participate to the validation. In all, twenty participants were selected and invited to categorise the list of radiotherapy interventions according to their individual interpretation of the decision tree.

² Value-Based Radiation Oncology (VBRO) – is an ESTRO/ECF – HERO project aiming to develop a framework to define value of radiation oncology to reflect the specificities of the treatment, allowing for optimisation of patient access to high-value developments in radiotherapy. Find more on [https://www.estro.org/Science/Activities/Value-Based-Radiation-Oncology-\(VBRO\)](https://www.estro.org/Science/Activities/Value-Based-Radiation-Oncology-(VBRO)).

Table 1

Mixed-method design in four phases to develop and validate a categorisation system for radiotherapy interventions, using a decision algorithm. For each phase, key methodologies, participants and results are shown.

Time period	Phase of development	Methods	Participants	Results
February 2022 – November 2022	Phase 1 Identifying and analysing existing categorisation systems	Systematic literature review Critical appraisal and categorisation exercises of identified categorisation systems	VBRO steering committee	Identification of essential radiotherapy-specific characteristics for categorisation
December 19th, 2022	Phase 2 Defining meaningful categories and core decision-making questions	In-person co-creation workshop	VBRO steering committee	(1) Decision-making questions to assist categorisation (2) Definition of categories
January 2023 – July 2023	Phase 3 Adapting and synthesising the categories into a decision algorithm	Iterative rounds of categorisation exercises, analysis and discussion, supported by quantitative and qualitative data	VBRO steering committee	(1) Decision algorithm in the form of a categorisation decision tree (2) Finalised definition of categories
August 2023 – March 2024	Phase 4 Validating the categories and categorisation system	Quantitative and qualitative analyses of validation exercises Data analysis from a bibliometrical study of radiotherapy research Final validation and acceptance	VBRO steering committee Radiation oncology community through ESTRO	Validated categorisation decision tree and categories

Abbreviations: VBRO – value-based radiation oncology project; ESTRO – European Society for Radiotherapy and Oncology.

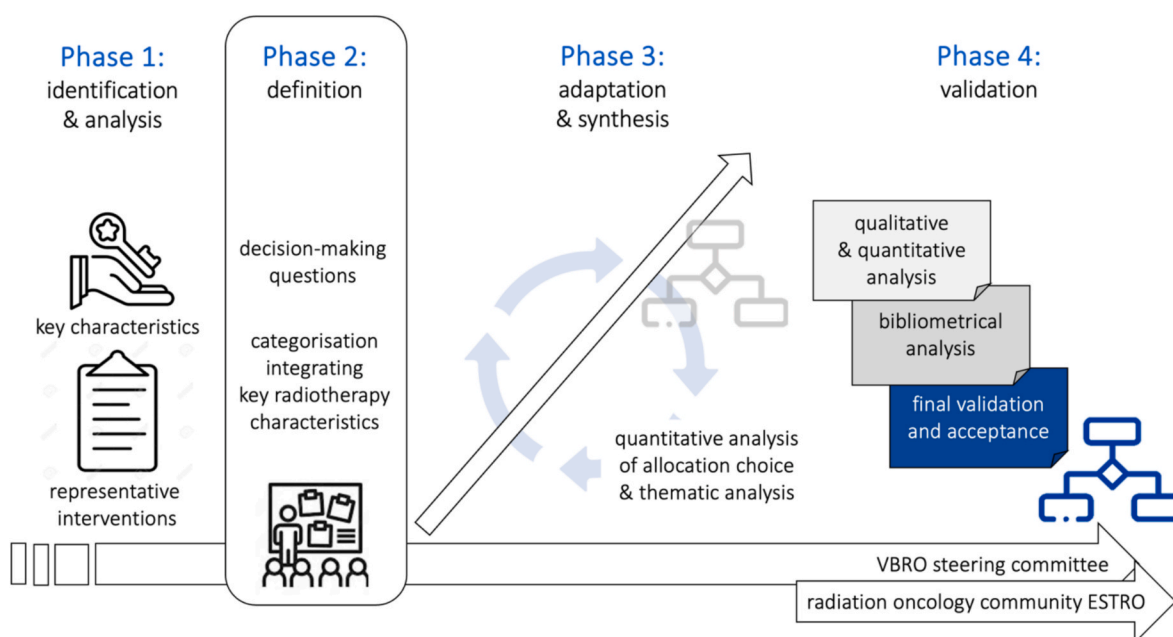


Fig. 1. Visual representation of the multi-method approach to develop the categorisation system and define the categories.

A survey with open questions and statements with a five-point Likert scale of agreement was added to evaluate the defined categories and the decision system. (See Addendum for survey and results). The Survey-Monkey® tool was used, statistical analysis was done using IBM® SPSS® software (version 29.0.2.0).

Quantitative evaluation by data analysis from a bibliometrical study

In parallel, a bibliometric analysis of radiation therapy research outputs for the 23 radiotherapy interventions between 2012–2022 was performed in the Web of Science database, building on a previously published methodology. [7] This analysis identified the predominant endpoints and study designs used to appraise these interventions in the literature. Statistical analysis was done using R statistical software (version 4.3.1).

Final validation and acceptance by the steering committee

Building on the evaluation by the European radiation oncology stakeholders and the bibliometrics data (cf. 4.1 and 4.2), the

categorisation decision algorithm and decision tree were finalised by the steering committee.

Each change of the category definitions and categorisation decision tree was discussed and approved by consensus. Final validation by the steering committee was obtained through consenting the categorisation of each intervention in the representative list (minimum 5/6 consensus).

Results

Categories of radiotherapy interventions defined by the decision algorithm

Four distinct categories of radiotherapy interventions are defined, based on their primary aim (see Table 3 for an overview with representative interventions per category):

1. Drug-centred radiation interventions:

Aim to optimise the therapeutic ratio by generating better biological effectiveness of the radiation interventions, by combining drug therapy with radiation therapy.

Table 2
List of 23 radiotherapy interventions to represent the diversity across the radiotherapy spectrum.

List of 23 representative radiotherapy interventions
Perform AI-based planning
Perform AI-guided autocontouring
The Cyberknife machine
Performing breathhold (for motion management)
Insertion of fiducial markers
Perform a 4D CT simulation
High-dose-rate brachytherapy
Hypofractionated treatment
Image-guided radiotherapy (IGRT)
Concurrent immunotherapy with radiotherapy treatment
Spatially fractionated radiotherapy (LATTICE)
The MR-Linac machine
Online adaptive radiotherapy
Use of a prone breast board
Proton beam radiotherapy treatment
Use of a rectal spacer
Stereotactic Body Radiotherapy
Addition of a radiosensitiser to radiotherapy treatment
Surface-guided radiotherapy (SGRT)
Stereotactic radiosurgery
Tomotherapy or helical tomotherapy
FLASH radiotherapy treatment
Volumetric modulated arc therapy

Abbreviations: 4D – four dimensional; AI – artificial intelligence; MRI – Magnetic resonance imaging.

These can include combination therapies with radiosensitisers or systemic oncology agents, typical examples are radio-immunotherapy or radio-chemotherapy.

2. Radiation-centred radiation interventions:

Aim to optimise the therapeutic ratio of the radiation delivered, by optimising its biological and/or dosimetric properties thus impacting the effect of the radiation on the tumour and/or the healthy tissues.

Examples of modes of action are dose escalation or higher biologically effective dose delivered to the clinical target, radiation delivering a reduced dose to the normal tissues by better shaping the radiation delivered or tighter margins around the target. Typical examples, often conjointly exploiting different modes of action, are proton radiotherapy, hypofractionation, MRI-linac, or high dose-rate brachytherapy.

Table 3
Four categories of radiotherapy interventions with representative interventions, categorised using the decision tree.

Category of interventions	Interventions
Drug-centred radiation interventions	Radio-immunotherapyRadiosensitiser
Radiation-centred radiation interventions	Cyberknife FLASH radiotherapy High-dose-rate brachytherapy Hypofractionation MRI-LinacOnline adaptive radiotherapy Proton radiotherapy Stereotactic radiosurgery Stereotactic Body radiotherapy Spatially fractionated radiotherapyTomotherapy Volumetric modulated arc therapy
Radiation-enabling radiation interventions	4D CT simulation Deep inspiration breathhold Fiducial markers Image-guided radiotherapy Prone breast boardRectal spacer Surface-guided radiotherapy
Operational radiation interventions	AI-based autocontouring AI-based planning

3. Radiation-enabling radiation interventions:

Aim to improve outcomes and experience of the treatment on the patient level by improving accuracy, precision or patient set-up, but do not have the core aim of optimising the biological and/or dosimetric properties of the radiation in itself.

This includes interventions that do not directly impact the radiation received by the patient but move the organs at risk out of the target area, or interventions that improve patient positioning or experience during treatment. Examples are rectal spacers, a prone breast board or open-face masks.

4. Operational radiation interventions:

Aim to make a change at the organisational level or in the operational workflow.

These can include products, resources, processes or services improving the efficiency or quality of the operational workflow and/or optimising workplace organisation. Typical examples are AI-based auto-contouring, or a patient identification system using face recognition.

The decision algorithm guiding the categorisation of radiotherapy interventions

The categorisation decision algorithm, graphically represented by a decision tree (Fig. 2), consists of a sequence of decision-making questions, ('decision nodes'; indicated in light blue and numbered 1–5). Depending on the answer for each of these questions, an arrow leads to a subsequent question or one of the four endpoint categories (indicated in dark blue), in which any given radiotherapy intervention will be categorised.

Defining whether the intervention primarily applies to the patient or organisational level.

In the first decision node (Fig. 2 – decision node 1), RO interventions are separated based on their core aim, focussing on either the patient-level or the organisational level.

Patient-level interventions aim to make a change for the patient specifically, by improving outcomes or patient experience and are further classified into different endpoint categories through a series of decision node questions.

Other interventions specifically aim to make a change at the organisational level or in the operational workflow. These interventions can be categorised in the endpoint category '**operational radiation interventions**'.

Defining whether the patient-level innovation is primarily based on a specific technology.

The subsequent decision node (Fig. 2 – decision node 2 – *Is the intervention a type of equipment, device or consumable?*) is used to further categorise patient-level interventions by identifying technologies, meaning all interventions that are considered a type of equipment, device or consumable. These are typically (but are not limited to) items to be purchased. Technologies are not a decision tree endpoint category, but are further classified into different categories through a series of decision node questions.

Defining whether the technology has a primarily clinical or operational aim.

If the core aim of a technology is to optimise the therapeutic ratio of the radiation delivered to the patient, that is enhancing local tumour control and/or decreasing normal tissue damage, by optimising the biological and/or dosimetric properties of the radiation compared to the current standard of care, then the technology is considered a clinical intervention. Devices or consumables improving the accuracy, precision or patient experience are also considered clinical interventions. The decision node 3 in Fig. 2 (*Is the core aim of the intervention to optimise the therapeutic effect of the treatment?*) differentiates the clinical from the operational interventions. Clinical interventions are not a decision tree

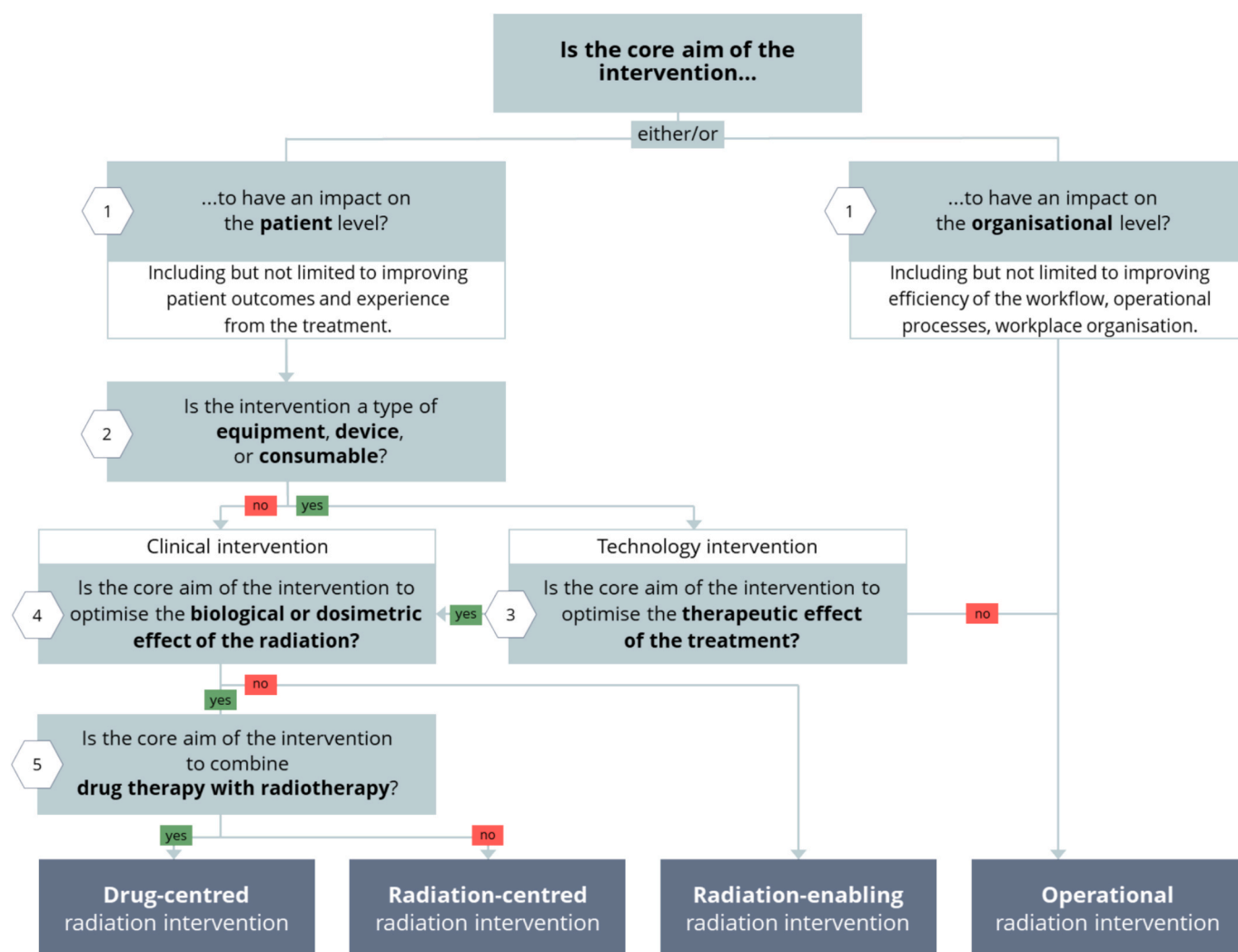


Fig. 2. Graphic representation of the categorisation decision tree for radiotherapy interventions. Decision node questions are indicated in light blue, decision tree endpoint categories are indicated in dark blue. Please refer to the full text of the manuscript for additional information on the decision nodes and examples to support categorisation of an innovation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

endpoint category and are further classified into different categories through a series of decision node questions. In contrast, if the technology intervention aims to change the operational processes or workflow efficiency at an organisational level, it is considered an ‘**operational radiation intervention**’, and categorised in this endpoint category (see above).

Defining how the intervention exerts its clinical impact.

Clinical interventions aim to achieve an optimised therapeutic ratio and are classified through a series of decision node questions (*Is the core aim of the intervention to optimise the biological or dosimetric effect of the radiation?* – decision node 4 and *Is the core aim of the intervention to combine drug therapy with radiotherapy?* – decision node 5) into one of three categories: ‘**drug-centred radiation interventions**’, ‘**radiation-centred radiation interventions**’, or ‘**radiation-enabling radiation interventions**’, all representing endpoint categories of the decision tree.

Validation of the definition process of categories and categorisation system

Qualitative and quantitative evaluation by representative stakeholders of the European radiation oncology community

Eighteen out of twenty invited participants (response rate 90 %) completed the categorisation exercise and survey. (See [Addendum](#)

[Table 1](#) for participant information) A majority agreed that the main categories (technology, clinical, operational) and the subcategories for clinical interventions (radiation-centred and radiation-enabling) were sufficiently distinct groups (respectively 67 % and 72 % of participants). Wording of all decision node questions was considered as (sufficiently) clear, with approval rates of the questions ranging between 67 %-85 %. (See [Addendum Tables 2-3](#) for full results).

Quantitative evaluation by data analysis from a bibliometrical study

A Fisher-Exact test showed significant differences in the proportion of endpoints and study designs per category (all p-values < 0.001), supporting the hypothesis that each categories requires a tailored appraisal. (See [Addendum Tables 5 and 6](#); full details of the analysis are published in an accompanying paper). [24]

Categorisation of the reference radiation interventions used to build the algorithm

Each intervention of the representative list was categorised using the decision tree, as a final validation of the categorisation algorithm and definition of the categories. See [Table 3](#) for the resulting categorisation.

Discussion

The multi-method approach used in this project, resulted in a decision algorithm to categorise all radiotherapy interventions, through a series of decision node questions, into four categories. Gaining a better understanding of these different categories and their interrelation with optimum study design for evaluation, outcomes, and magnitude of benefit, is essential in building a value-based framework for radiation oncology. The ultimate aim of such a value-based framework is to facilitate timely access for patients to beneficial innovations, by better appraisal of clinical evidence and cost incurred, thus supporting clinical implementation and healthcare policy decision-making. [5,6,14–16,22].

At present there is no widely accepted categorisation system for radiotherapy interventions, and only a limited number of systems were identified through a literature review that take into account radiotherapy-specific characteristics. [16,22,25–27] Several aspects of the methodology presented in this paper strengthen the validity of the proposed categorisation system compared to the other systems found in the literature.

Whereas previous systems and categories may have caused ambiguity in interpretation by using common terminology without clear definition or offering only limited category descriptions without additional information to support classification choice for a given intervention, this project uses a logical decision algorithm supporting categorisation, and a clear description with examples of well-known radiotherapy interventions for each category. These categorisation algorithm and category definitions were developed using a stepwise multi-method approach based on an established framework, integrating qualitative and quantitative data in multiple rounds of revision, improvement and validation.

Additionally, the VBRO project as a whole, and the development of this categorisation system specifically, is framed within and supported by previous research and recommendations from the ESTRO-HERO project. Radiation oncology community representation was ensured through the multidisciplinary steering groups of ESTRO as well as involvement of a broader group of stakeholders during validation. Throughout all phases, stakeholders were aware of the purpose of the categorisation system: to be integrated into a value-based appraisal tool for policy-making and reimbursement decisions. This methodology and stakeholder involvement contrasts with existing categorisation systems, which are based mostly on expert opinion, supported by a limited group only or lack a clear methodology.

While this project in our view presents the first consistent categorisation system for radiotherapy interventions, building upon a rigorous methodology, further considerations are needed for the development of the VBRO project.

A first caveat is that the examples of radiotherapy interventions used in the development process are a mixture of ‘proven’ innovations and true ‘emerging’ innovations, as described by Borràs et al. [13] While in essence the VBRO project aims at a critical appraisal of emerging innovations in view of supporting clinical implementation and policy decision-making, it is important to note that what is considered proven in one jurisdiction, may still be seen as emerging innovation in others. Along the same line, future work will have to explore if the described categorisation holds true in different economic contexts, such as for the implementation of new radiotherapy interventions in underserved low- and middle-income countries, where the innovation gap may be overshadowed by a major access gap. [16,28].

Certain innovations may also appear to fit into more than one category, depending on their claimed benefit, which in turn may be perceived differently by various stakeholders – the healthcare provider, the manufacturer, the patient, or the regulatory authority. While a solid knowledge of radiation oncology was needed to develop a categorisation system of radiotherapy interventions, and its embedding in ESTRO favoured the European perspective, further work will evaluate the impact of different stakeholders, validate it and support its adoption.

Additional stakeholders will include the radiation oncology community beyond Europe, other oncology specialty experts such as medical oncologists, patients, policy-makers and industry partners. [16].

This categorisation system is intended to inform appraisals that support implementation or reimbursement decisions, with implications that will materialise in the next steps of the VBRO project. For each category, meaningful benefit will be determined by identifying the appropriate endpoints and level of evidence. By recognising high-value innovations, their clinical implementation can be prioritised or facilitated through regulatory mechanisms such as reimbursement. In addition, a structured appraisal framework may guide towards the best methodology and design of future studies, in keeping the expected benefits, facilitate comparison across studies and increase alignment of research efforts with patient and societal priorities. Hence, if different benefits are claimed, this will also impact the level of evidence and the outcomes required to allow correct appraisal. Future development of the appraisal framework will need to consider how innovations with multiple or variable anticipated benefits can be effectively appraised.

Last but not least, this work represents a first methodologic exercise, but the system will need to demonstrate its merit. Future relevance will need to be ensured by extensive field testing and regular evaluations in real-world settings, also beyond the typically high-income European context, while further improvements and/or adaptations may be required in the rapidly evolving field of radiation oncology.

Conclusion

This study presents a categorisation system for radiotherapy interventions, developed using a robust multi-method approach. Providing clarity on the definition of different categories of radiotherapy interventions, it forms a solid base to build a value-based framework for radiation oncology. This VBRO framework aims to facilitate evidence-based decision-making in healthcare policy and clinical practice, ultimately improving patient access to beneficial emerging radiotherapy innovations. In the next steps of the ESTRO-HERO value-based radiation oncology project, the required outcomes, thresholds of benefit, and levels of evidence will be determined for each of the four defined categories. [16].

CRedit authorship contribution statement

M. Vandemaele: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Conceptualization. **P. Blanchard:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **J.M. Borràs:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **M. Leech:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **M. Aznar:** Writing – review & editing, Investigation, Formal analysis, Conceptualization. **A. Aggarwal:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Y. Lievens:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MV acknowledges the support of the Value-based Radiation Oncology (VBRO) project by the European Society for Radiotherapy and Oncology (ESTRO) and the ESTRO Cancer Foundation (ECF). This project is supported by a grant from Elekta and Varian. ESTRO and ECF support the chair ‘ESTRO Value-based Radiation Oncology’ at the faculty of Medicine and Health Sciences of Ghent University. YL is former president of ESTRO, co-chair of the ESTRO-HERO project and promotor of the UGent

Chair ‘ESTRO Value-based Radiation Oncology’, which is financially supported by the ESTRO Cancer Foundation. She receives financial support from Astra Zeneca, for work unrelated to the VBRO research. MA acknowledges the support of the Engineering and Physical Research Council (Grant number EP/T028017/1). PB, JB, ML, AA have no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2025.111167>.

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