An international modified Delphi study to prioritise levels of evidence and outcomes to appraise radiotherapy innovation in the ESTRO Value-Based Radiation Oncology framework

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This international Delphi study, led by the European Society of Radiation Oncology as part of their Value-Based Radiation Oncology programme, brought together key experts from the radiation oncology community to build consensus on both the level of evidence and the endpoints that are essential to support clinical implementation or policy decisions (eg, reimbursement) for different types of radiotherapy innovations. Although randomised trial evidence remained a high priority across most innovation types, other evidence, such as high-quality prospective observational studies or alternative designs such as pragmatic trials, was found to be a suitable alternative in specific scenarios. In addition, the importance of a broader set of clinical endpoints beyond overall survival was acknowledged, including quality of life, local control, and functional endpoints. These consensus criteria aim to inform the development of a structured appraisal framework for radiotherapy innovation, guiding health-care providers and policy makers in identifying and promoting high-value radiotherapy that offers meaningful benefit to patients and supports implementation.

Introduction

Radiotherapy is an essential pillar in cancer control, with innovations continuously being developed that promise considerable patient benefit.[1,2] Although some innovations deliver substantial improvements, others offer only marginal gains, risking inefficient resource allocation or exposing patients to suboptimal care.[3,4] To facilitate timely access to high-value care for patients and preserve health-care sustainability and accessibility, it is essential to identify those innovations that bring meaningful clinical benefit.[5]

Appraisal of radiotherapy is challenging, with a scarcity of high-level evidence: only 5·1% of radiotherapy research outputs are clinical trials, and a substantial number of studies are retrospective in design.[6,7] This paucity of evidence reflects structural barriers to conducting clinical research in radiotherapy, such as the need for substantial up-front investments (eg, for linear accelerators with specialised features), operator dependency and associated learning curves, or scarce radiotherapy research funding, which only accounts for 2·8% of global cancer research funding.[6,8,9]

Radiotherapy research is further complicated by the diversity of interventions, spanning novel equipment, new dose fractionation schemes, particle therapy, and radiotherapy-drug combinations, to consumables such as immobilisation masks. At the patient level, radiotherapy innovations typically aim to optimise treatment accuracy or precision, or modify the delivered dose, to improve local control or decrease side-effects, thus improving the therapeutic ratio.[10] These endpoints can take a long time to convert into traditional outcomes, such as overall survival, which have been typically considered as the primary outcome of clinical efficacy in cancer trials to date. Furthermore, some innovations might specifically aim to improve organisational workflows by reducing personnel time and costs, or to improve the quality and safety of treatment planning and delivery, while maintaining clinical outcomes.

Considering the sheer diversity of innovations and the challenge this poses for designing trial methodologies and showing patient and societal benefits, the diversity of evidence generation should also be considered. Should every innovation be supported by a randomised controlled trial (RCT), or might other levels of evidence be considered to justify adoption into clinical practice?[8,11] At present, market entry standards for radiotherapy technologies are low, requiring only safety evidence, and there is no consensus within the professional radiotherapy community on the appropriate level of evidence or endpoints required to support clinical implementation of innovations.[8] The absence of generally accepted standards results in a paucity of high-level evidence, delaying clinical adoption or creating a disconnection between innovative care and reimbursement authorisation, which typically relies on clinical trial evidence.[12–14]

To avoid ongoing clinical and policy stasis across Europe, and to support adoption and regulatory approval of radiotherapy innovations, clear criteria need to be established to define the clinically meaningful benefit of these innovations. This Policy Review aimed to achieve consensus on priority study designs and endpoints for different categories of innovation, in view of identifying high-value interventions. To this end, we conducted a unique Delphi consensus study that engaged the international professional radiation oncology community through the European Society for Radiotherapy and Oncology (ESTRO).

Methods

Design

A modified Delphi study was designed, following the CREDES recommendations, to establish consensus within the radiation oncology community on essential

Lancet Oncol 2026; 27: 160–69

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See Online for appendix 1

study designs and endpoints for appraising different categories of radiotherapy innovations.[15] The multistage process involved structured questionnaires, with four characteristic features: anonymity, iteration with controlled feedback, statistical group response, and expert input.[15]

Two rounds of online voting were done, followed by a third round during an in-person conclusive meeting, which included a semi-structured group discussion. The second part of this meeting was dedicated to discussion and voting of a rank order for all items that reached the consensus threshold in Delphi rounds 1–3 (figure 1).

Categories of radiotherapy interventions presented in the Delphi study

A categorisation algorithm was developed through a multistakeholder mixed-method approach in the ESTRO Value-Based Radiation Oncology (VBRO) project,[16] defining four categories of radiotherapy interventions (appendix 2 p 2). These interventions consisted of three categories aimed at improving outcomes or experiences at the patient level: drug-centred radiotherapy innovations, which combine drug therapies with radiation (eg, radio-immunotherapy or radiosensitisers); radiation-centred radiotherapy innovations (eg, hypofractionation or stereotactic body radiotherapy, delivered by different technologies), which aim to optimise the therapeutic ratio and typically result in better local control or reduced toxicity; and radiation-enabling radiotherapy innovations (eg, rectal spacers or prone breast boards), which aim to improve outcomes and the treatment experience through enhanced accuracy or better patient setup. The fourth category was operational radiotherapy innovations, which are not directly aimed at patient impact but instead seek to make a change at the organisational level or within the operational workflow (eg, artificial intelligence-based auto-contouring). Each category represents a group of interventions requiring a specific level of evidence and distinct endpoints to be considered valuable. These categories were presented to the participants, including background information and examples for clarity.

See Online for appendix 2

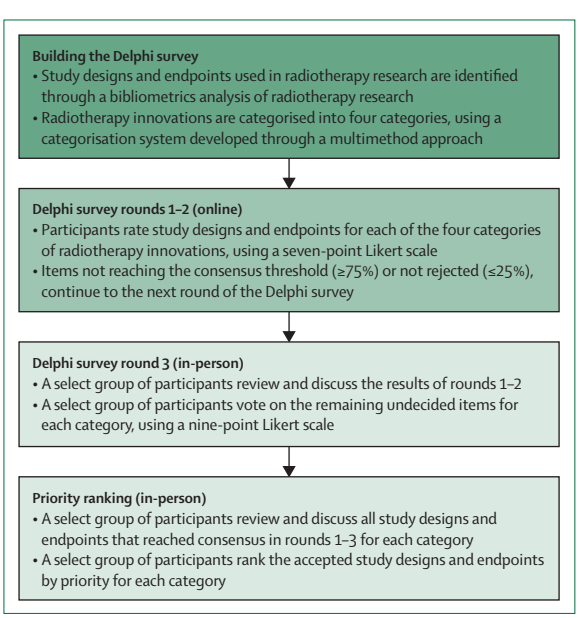

Figure 1: **Overview of modified Delphi study process**

Study designs and endpoints presented in the Delphi study

Before the Delphi study, a bibliometrics analysis of radiotherapy literature from Jan 1, 2012, to Dec 31, 2022 was done in the Web of Science database. This robust literature analysis aimed to identify different types of study design and endpoints used in the appraisal of radiotherapy interventions.[17]

The identified study designs were grouped into eight different types: phase 1, 2, 3, and 4 trials; prospective observational design (eg, prospective cohort studies); retrospective observational design (eg, retrospective cohorts); preclinical design (eg, in vitro studies, phantom studies); and alternative study designs. The latter group included novel study designs, methodologies, or statistical approaches that offer opportunities for the inclusion of a broader set of patients, increase the efficiency of accrual and evidence generation, and use increasingly high-quality real-world data. Examples include adaptive trial designs, pragmatic trials, or trial emulation methods using real-world data, which address questions in a routine clinical context and use inclusive populations to provide high external validity.[18,19]

Endpoints were divided into four main groups (clinical endpoints; toxicity and quality-of-life endpoints; operational, structural, or time-related endpoints; and technical, quality, and safety endpoints), within which there were 12 types of endpoints in total (appendix 2 p 3). These study designs and endpoints were presented to the participants in the Delphi survey, with examples taken from literature for clarity.

Part 1: Delphi survey online rounds 1 and 2

Participants

To ensure representation of the radiation oncology community, participants were recruited from the ESTRO society membership. An invitation email was sent to all 120 active members, identified as ESTRO Board members, Scientific Council chairs, and committees (including the Clinical, Physics, Biology, Radiation Therapist, Groupe Européen de Curiethérapie-ESTRO, Young, Guidelines, National Societies and Radiation Oncology Safety and Quality Committees), which represent the different professional backgrounds in the radiation oncology community, such as radiation oncology, medical physics, radiation therapy, and radiation biology.

Participants were required to consent before entering the survey. Participants completing round 1 were invited by email to participate in round 2. The questionnaires for both rounds were created in the Qualtrics survey suite (version: April, 2024). The investigators participating in the Delphi study (AA, YL), were blinded to interim results of the online rounds while both rounds were ongoing.

Data collection

Participants rated the relative importance of the different study designs and endpoint types with respect to supporting clinical implementation and policy decisions across the four categories. A seven-point Likert scale was used, ranging from strongly disagree to strongly agree on the statement: to what extent do you agree [this study design or endpoint type] is essential for assessment of [this category of radiotherapy innovation].

Consensus was defined as 75% or higher of respondents indicating strongly agree or agree (Likert scale scores 6–7), moving these study designs and endpoint types to the priority ranking stage. Items were rejected if 25% or fewer of participants indicated Likert scale scores 6–7. Items not reaching consensus or not rejected, with 25–75% of respondents scoring Likert scale scores 6–7, proceeded to the next round for reconsideration.

Open-text feedback from participants was used to provide clarifying information or examples in round 2. In round 1, participants also completed a short survey with sociodemographic and professional activity questions.

Part 2: in-person workshop including Delphi round 3 and priority ranking exercise

Participants

The third Delphi round was done during an in-person meeting with a select number of invited participants to facilitate interactive discussion. Only participants who completed both online Delphi rounds were eligible (N=41). Further selection of participants was done considering representation of the radiation oncology community through professional background (radiation oncology, medical physics, radiation therapy, radiation biology, etc), and geographical region.

Delphi round 3

The results of rounds 1 and 2 were openly discussed per category, following a structured agenda and timeline. Any rejected items from rounds 1 and 2 with borderline scores were reviewed by the participants and could be reconsidered for voting in round 3 if 75% or more of participants agreed. Participants then individually rated the study designs and endpoints for which consensus had not been reached in the first two rounds for each innovation category, using a nine-point Likert scale (ranging from should not be considered to highest priority) via the online Wooclap platform (version: June, 2024). Consensus was defined as 75% or more of respondents indicating highest priority, high priority, or moderately high priority (Likert scale scores 7–9). If these scores were achieved for any of the items for which consensus had not been achieved in rounds 1 and 2, these items then moved into the priority ranking phase.[20] Any items that did not achieve this score were dropped.

For the **Qualtrics survey suite** see http://www.qualtrics.com

Priority ranking exercise

All study designs and endpoints reaching consensus in rounds 1–3 advanced for ranking per category, in view of their importance to support clinical implementation and policy decision making. Participants individually ranked a top three study designs and a top five endpoints, with the online Wooclap platform. Five ranking options were put forward for the endpoints after conclusion of the Delphi survey rounds because of the large number of endpoint types that had achieved consensus.

For analysis of the ranking process, the data were scored such that an item that was ranked among the most important (eg, rank one out of five) was given the highest score of six points, a second priority score yielded five points, and so on. Each item score was then summed based on all responses, and summary scores and respective rankings were developed for study designs and endpoints for each category. If two items had an equal summary score, they were ranked based on the number of participants scoring them as the highest priority.

Detailed notes and audio recordings of the meeting were reviewed systematically and discussed by the authors to ensure that key themes and arguments discussed by participants were included in this Policy Review.

Results

Delphi rounds 1–3

Two consecutive online rounds took place in 2024, round 1 from April 1, to April 24, and round 2 from May 1 to May 22. 48 (40%) of 120 invited active ESTRO members participated in round 1, and 41 participants also completed round 2. Participants in round 1 represented 16 different countries across the EU plus Switzerland, the UK, and Türkiye. Participants had various professional backgrounds, with nine (19%) having 6–15 years and 39 (81%) over 15 years of professional experience. Participants in round 2 were found to be similar. 17 participants were invited to join the in-person meeting on June 27, 2024, of which 13 (76%) attended (appendix 2 p 4).

Table 1 presents an overview of the consensus scores for study designs in the subsequent Delphi rounds, and table 2 presents an overview of endpoint types. After three Delphi rounds, for drug-centred interventions, three study designs and seven endpoint types reached consensus and were advanced to the priority ranking exercise undertaken at the face-to-face workshop. For radiation-centred interventions, four study designs and 12 endpoint types were moved to the ranking exercise;

For the **Wooclap platform** see http://www.wooclap.com

	Drug-centred interventions				Radiation-centred interventions				Radiation-enabling interventions				Operational interventions			
	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=12)*	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=12)*	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking
Phase 3 trial	46 (96%)	NA	NA	1	34 (71%)	31 (76%)	NA	1	19 (40%)	15 (37%)	10 (77%)	3	16 (33%)	12 (29%)	10 (77%)	3
Phase 2 trial	44 (92%)	NA	NA	2	33 (69%)	33 (80%)	NA	3	20 (42%)	19 (46%)	9 (69%)	NA	17 (35%)	10 (24%)	NA	NA
Phase 1 trial	39 (81%)	NA	NA	3	23 (48%)	20 (49%)	2 (17%)	NA	13 (27%)	11 (27%)	4 (31%)	NA	10 (21%)	NA	NA	NA
Prospective observational design	17 (35%)	24 (59%)	4 (33%)	NA	31 (65%)	31 (76%)	NA	4	34 (71%)	26 (63%)	11 (85%)	2	30 (63%)	26 (63%)	13 (100%)	2
Retrospective design	11 (23%)	NA	NA	NA	18 (38%)	21 (51%)	3 (25%)	NA	18 (38%)	19 (46%)	4 (31%)	NA	17 (35%)	19 (46%)	3 (23%)	NA
Preclinical design	21 (44%)	21 (51%)	1 (8%)	NA	13 (27%)	11 (27%)	3 (25%)	NA	16 (33%)	13 (32%)	4 (31%)	NA	18 (38%)	17 (41%)	4 (31%)	NA
Alternative study design	13 (27%)	10 (24%)	NA	NA	22 (46%)	16 (39%)	10 (83%)	2	19 (40%)	15 (37%)	12 (92%)	1	19 (40%)	16 (39%)	10 (77%)	1

Study designs that reached consensus throughout the Delphi rounds 1–3 were included in the subsequent ranking process. The ranking order as voted by participants is presented in the ranking column. NA=not applicable. *In these rounds, one participant was not yet present due to travel delays.

Table 1: **Overview of consensus scores (% agreement) for study designs per category of radiotherapy innovations in Delphi rounds 1–3**

	Drug-centred interventions				Radiation-centred interventions				Radiation-enabling interventions				Operational interventions			
	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking	Round 1 (N=48)	Round 2 (N=41)	Round 3 (N=13)	Ranking
Local or locoregional endpoints	41 (85%)	NA	NA	4	47 (98%)	NA	NA	1	28 (58%)	21 (51%)	12 (92%)	3	17 (35%)	13 (32%)	10 (77%)	5
Systemic progression endpoints	44 (92%)	NA	NA	5	30 (63%)	26 (63%)	12 (92%)	7	8 (17%)	NA	NA	NA	9 (19%)	NA	NA	NA
Overall survival*	44 (92%)	NA	NA	1	39 (81%)	NA	NA	2	11 (23%)*	NA	10 (77%)	9	9 (19%)	NA	NA	NA
Toxicity endpoints	42 (88%)	NA	NA	2	47 (98%)	NA	NA	3	42 (88%)	NA	NA	1	19 (40%)	10 (24%)	NA	NA
Functional endpoints	36 (75%)	NA	NA	7	48 (100%)	NA	NA	6	34 (71%)	31 (76%)	NA	5	16 (33%)	12 (29%)	6 (46%)	NA
Quality-of-life endpoints	41 (85%)	NA	NA	3	44 (92%)	NA	NA	5	37 (77%)	NA	NA	7	14 (29%)	10 (24%)	NA	NA
Time-related endpoints	5 (10%)	NA	NA	NA	36 (75%)	NA	NA	12	35 (73%)	31 (76%)	NA	10	41 (85%)	NA	NA	4
Operational and structure endpoints	5 (10%)	NA	NA	NA	36 (75%)	NA	NA	8	34 (71%)	32 (78%)	NA	8	39 (81%)	NA	NA	6
Resources and costs endpoints	27 (56%)	23 (56%)	10 (77%)	6	38 (79%)	NA	NA	10	37 (77%)	NA	NA	6	44 (92%)	NA	NA	3
Physics and planning endpoints	3 (6%)	NA	NA	NA	37 (77%)	NA	NA	11	34 (71%)	24 (59%)	7 (54%)	NA	31 (65%)	22 (54%)	10 (77%)	7
Accuracy endpoints	7 (15%)	NA	NA	NA	40 (83%)	NA	NA	4	39 (81%)	NA	NA	2	35 (73%)	31 (76%)	NA	1
Quality of care endpoints	9 (19%)	NA	NA	NA	37 (77%)	NA	NA	9	37 (77%)	NA	NA	4	33 (69%)	24 (59%)	13 (100%)	2

Endpoints that reached consensus throughout the Delphi rounds 1–3 were included in the subsequent ranking process. The ranking order as voted by participants is presented in the final column. NA=not applicable. *Overall survival was reconsidered for round 3 of the Delphi consensus by agreement of 75% or more of participants, as clarified in the methodology.

Table 2: **Overview of consensus scores (% agreement) for endpoints per category of radiotherapy innovations in Delphi rounds 1–3**

for radiation-enabling interventions, three study designs and ten endpoint types; and for operational interventions, three study designs and seven endpoint types.

Ranking of consensus items

The results of the Delphi rounds were discussed, after which participants were asked to individually rank their top three study designs and top five endpoint types for each category. The resulting rank order of the accepted study designs and endpoint types for each category is shown in tables 1 and 2 and figures 2 and 3.

For drug-centred radiation interventions, the ranking order for the three accepted study designs (high to low) was phase 3 trials, phase 2 trials, and phase 1 trials. Of seven accepted endpoint types, the highest-ranking were overall survival, toxicity, quality of life, local or locoregional control, and systemic progression endpoint types.

For radiation-centred interventions, the four accepted study designs (high to low) were phase 3 trials, alternative study designs, phase 2 trials, and prospective observational designs. Out of twelve accepted endpoint types, the highest-ranking were local or locoregional, overall survival, toxicity, accuracy, and quality of life endpoint types.

The ranking of the three accepted study designs for radiation-enabling interventions (high to low) was alternative study designs, prospective observational designs, and phase 3 trials. The highest ranking out of ten accepted endpoint types were toxicity, accuracy, local or locoregional, quality of care, and functional endpoint types.

For operational interventions, the three accepted study designs (high to low) were alternative study designs, prospective observational design, and phase 3 trials. Of seven accepted endpoint types, the highest ranked were accuracy, quality of care, resources and costs, time-related, and local or locoregional endpoint types.

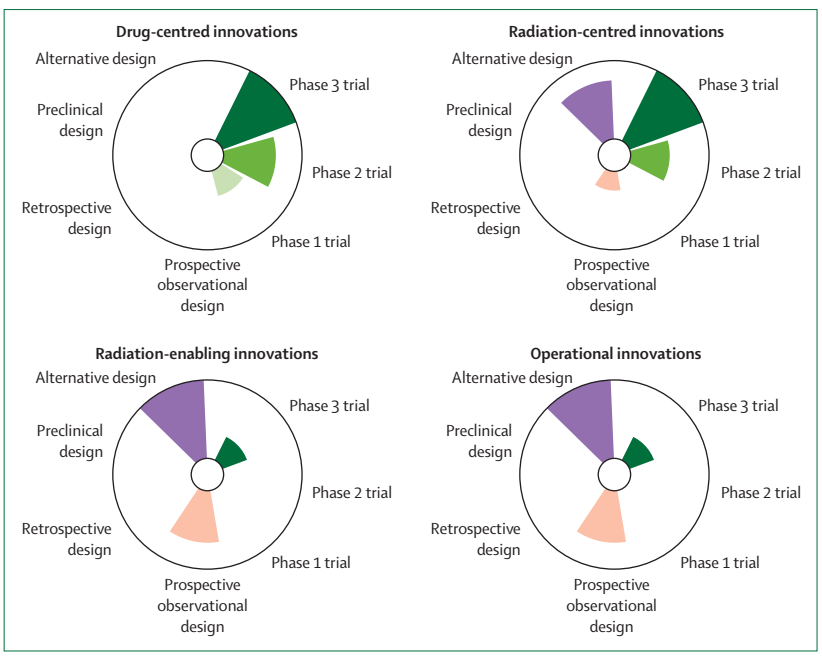

Figure 2: **Visual representation of ranking for study designs per category**

Discussion

To our knowledge, this study is the first to achieve consensus among the international radiation oncology community on the level of evidence and outcomes required to support clinical implementation and inform policy decisions regarding the regulatory approval and reimbursement of radiotherapy innovations. A key finding is the essential role of RCTs across all categories. For selected innovations or specific categories, prospective observational designs or alternative study designs were also considered as sources of essential evidence. In addition, showing meaningful benefit for an innovation requires a broad spectrum of endpoints, including overall survival, other clinical endpoints such as local control and functional endpoints, and operational endpoints.

Radiotherapy demand is rising rapidly due to demographic changes (ageing populations), new indications, and more personalised treatments (eg, radical metastasis directed radiotherapy for oligometastatic disease), and increasing possibilities for retreatment.[21–23] However, access to radiotherapy in general and to innovative care in particular remains a challenge. Many cancer patients with an evidence-based indication, in Europe and beyond, still do not receive the radiotherapy they need, and clinical implementation of innovative radiation therapy is often delayed or fails altogether.[2,24,25]

To optimise access to radiotherapy and allocate health-care resources most efficiently, various strategies have been developed to identify which interventions deliver value for money. One broad approach is to consider the value an innovation brings if introduced at scale. In this regard, value-based health-care—defined as outcomes that matter most to patients, achieved for the cost over the total cycle of care—has been increasingly used since its inception in 2010.[26] However, value-based frameworks that have shown merit in medical oncology, such as the European Society For Medical Oncology Magnitude of Clinical Benefit Scale, and the American Society of Clinical Oncology Value Framework, fall short for radiotherapy.[27,28] These frameworks fail to account for the diversity of radiotherapy innovations and the heterogeneity in evidence generation, nor do they capture all potential benefits of radiotherapy.[8,27,28]

Recognising the need for an appraisal tailored to radiotherapy, ESTRO launched the Value-Based Radiation Oncology project.[29] This Delphi study was conducted within this project, aiming to identify high-value radiotherapy and shed light on how the radiation oncology community values evidence and endpoints in different categories of radiotherapy innovations. For the category of drug-centred innovations, the ranking of study designs

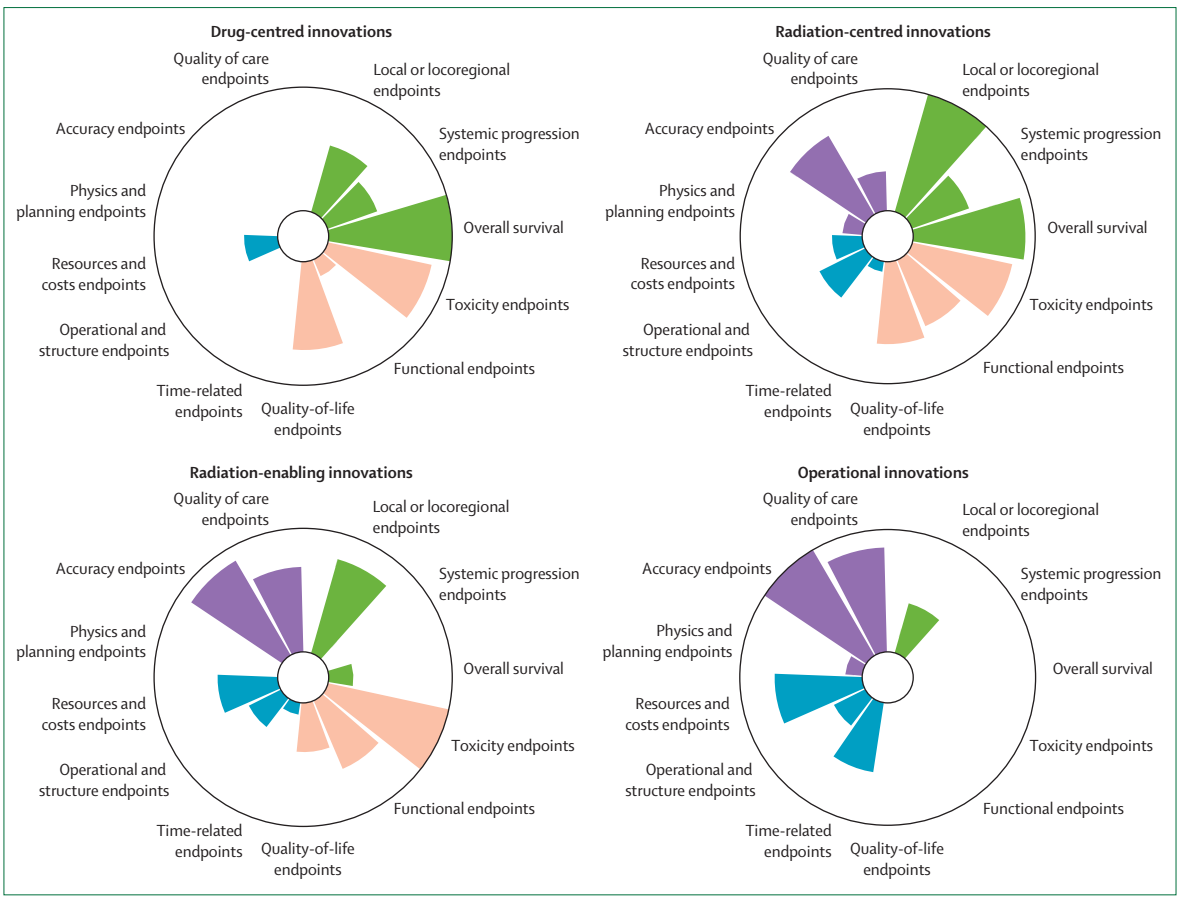

Figure 3: **Visual representation of ranking for endpoints per category**
The endpoints were grouped in 12 types, with four main groups. Green: clinical endpoints (local or locoregional endpoints, systemic progression endpoints, and overall survival); pink: toxicity and quality-of-life endpoints (toxicity endpoints, functional endpoints, and quality-of-life endpoints); blue: operational, structural, or time-related endpoints (time-related endpoints, operational and structure endpoints and resources and costs); and purple: technical, quality, and safety endpoints (physics and planning endpoints, accuracy endpoints, and quality of care parameters)

and endpoint types aligns with the typical appraisal of systemic therapies, emphasising phase 3 clinical trials.[27,28] In addition, participants recognised that earlier phase evidence (phase 2 or even phase 1 clinical trials) can influence clinical practice, as has been shown for drug-centred innovations in less frequent cancer types.[30,31]

For the other categories, participants moved beyond traditional evidence generation. Clinical trials were still identified as a priority in radiation-centred innovations; phase 3 trials, for example, are typically used to alter clinical practice in the high-incidence cancer types (eg, the FAST-FORWARD trial),[32] and phase 2 studies have shown merit in tumour types, indications, or technical innovations, where large trials are more difficult to execute. For example, evidence generation on stereotactic ablative radiotherapy as a proposed new radiotherapy standard of care in early-stage non-small cell lung cancer was initially hampered by the incremental implementation of the technique and the associated learning curves, as well as the typically frail and elderly patient population.[32–36] Subsequent accrual to RCTs comparing radiotherapy to surgery has been slow, with many studies closing prematurely, largely driven by patient and clinician preference for one modality or the other.[32–36] In the categories of radiation-enabling or operational innovations, by contrast, clinical trials could be reserved for stepwise innovations that bring substantial change to clinical practice, or innovations that pose considerable risks for patients (eg, the introduction of rectal spacers for prostate cancer).[37] In these categories, a more principal role was given to alternative study designs and prospective observational studies. An important observation from this Delphi study was that retrospective study designs and preclinical study designs did not reach consensus in any of the categories, indicating that the current level of evidence from such studies is not sufficient to change clinical practice or support reimbursement.

The results reflect an ongoing tension in radiation oncology: although RCTs remain the gold standard of evidence, their feasibility is often limited by practical and logistical constraints. To balance methodological rigour and timely access to high-value innovations, alternative

methodologies offering more pragmatic and affordable evidence generation are increasingly used to inform clinical practice and support policy decisions in radiotherapy.[6,11,13,38,39]

In this Delphi study, such novel methodologies or statistical approaches were included in the group of alternative study designs. Examples are master protocols such as umbrella trials, which are developed to simultaneously evaluate multiple interventions or populations. For example, the PLATO trial of personalised radiotherapy dose in anal cancer is a single integrated protocol comprising three separate trials, including a non-randomised phase 2, a randomised phase 2, and an integrated randomised seamless pilot/phase 2/phase 3 trial.[40] Other examples are cohort multiple randomised controlled trial designs or trial within cohort studies, such as the PeRA initiative (NCT03378856) or the E²-RADIatE SPRINT study (NCT06462963), in which real-world patient data are prospectively collected and allow for tailored integration of multiple RCTs, or trial emulation methods, which use large scale national datasets reflecting the true patient population and exploit real world variations in use of treatment options—eg, surgery versus radiotherapy for early stage lung cancer.[41] These methods are designed to evaluate safety, efficacy, or effectiveness and to minimise residual confounding. They bring the added benefit of enabling assessment of cost-effectiveness of treatment options with robust datasets and typical standards of care.[6,21]

High-quality prospective observational designs also offer pragmatic advantages over RCTs, and can provide a more inclusive or comprehensive perspective. Their potential in changing clinical practice in radiotherapy has been shown through multicentre prospective cohort studies such as the EMBRACE-I or the DBCG-IMN.[42,43] Acknowledging the complexity of prospective observational evidence generation in radiotherapy, the European Organisation for Research and Treatment of Cancer and ESTRO established the E²-RADIatE (NCT03818503) project, which will build large datasets of real-life clinical and technical radiotherapy data, from which new hypotheses can be drawn to be further analysed in clinical trials. Prospective observational studies are also increasingly used to address combined clinical and public health questions; for example, in the ARCHERY trial, in which artificial intelligence-based auto-contouring is appraised from clinical, quality, operational, and economic perspectives, in view of implementation in regions with scarce resources.[44] Finally, coverage with evidence development programmes—where provisional financing is made dependent on data collection—have been recommended to generate clinical and economic evidence for emerging radiotherapy innovations and have facilitated the introduction of stereotactic body radiation therapy in the health-care system in Belgium and the UK.[45–47] All in all, radiotherapy innovations require a blended approach to evidence generation, deciding on the most appropriate study designs, alone or in combinations, to prove the clinical efficacy or effectiveness of various interventions. Beyond overall study designs, other methodological aspects warrant consideration. Many radiotherapy trials use non-inferiority designs, for example to evaluate treatment side-effects, or non-comparative designs, especially for interventions aimed at improving efficiency of care.[8] These features might influence the level of evidence assigned to general study designs and require further investigation. Other factors potentially affecting the validity and robustness of studies, such as data quality, rigour of methodology design, or statistical analysis, should also be explicitly addressed when appraising the evidence.

For drug-centred innovations, priority endpoints again reflected appraisal of drug therapies, prioritising traditional clinical endpoints—eg, overall survival. The other patient-centred categories of radiation-centred and radiation-enabling innovations prioritised a broader range of clinical endpoints, reflecting that radiotherapy benefits are often achieved by reducing side-effects or preserving functionality.[8]

For operational innovations, prioritised endpoints aligned with the primary aim of these interventions—eg, increasing patient throughput or reducing treatment time. Still, clinical endpoints remained relevant, particularly in cases where safety or effect on the patient is relevant. This Delphi study also highlights that improving operational efficiency can enhance meaningful clinical benefit, as illustrated in hypofractionated treatment regimes, and that both clinical and operational endpoints should be considered when assessing such innovations.[45,48,49]

The prioritised endpoints in this Delphi study underscore a broader issue: showing benefit for locoregional treatments, such as radiotherapy, requires a range of endpoints, including locoregional control, side-effects, or function preservation. Assessing these endpoints generally requires extended follow-up or large sample sizes before they translate into survival or quality-of-life improvements, which can greatly delay trial results. Such endpoints, along with operational endpoints, are typically not included in value frameworks that focus on systemic therapies, resulting in ungradability or lower scores even for practice-changing trials such as the AMAROS trial or the CHHIP trial.[8,50,51] As the selection of endpoints is crucial for showing meaningful benefit, a broader set needs to be prioritised when designing clinical research or appraising innovations. Furthermore, given the uniqueness of radiotherapy practice changes and innovation, endpoint selection or the role of surrogate endpoints in endpoint selection for clinical trials warrants further exploration.[8,21,52] Finally, this Delphi consensus did not consider any differences in essential endpoints across different clinical scenarios or treatment intents, such as the oligometastatic setting or the distinction between curative and palliative intent.

The importance of these specific scenarios, in terms of appraisal to support clinical implementation or reimbursement, will need to be investigated to determine whether the endpoints defining meaningful benefit, as determined in this Delphi study, still hold for a broad range of settings.

Strengths and limitations

This Delphi study's strengths include the multidisciplinary representation from the European professional radiation oncology community. The target population was based on members elected for the committees and the board of the ESTRO society, assuring a wide representation of the professionals in leading roles of radiation oncology in Europe. Future work will involve engaging a broader international stakeholder group (including from outside of Europe) to discuss and validate the findings, with particular focus on bringing in experts from other backgrounds beyond the field of radiation oncology, such as other oncology specialists, policy makers, clinical trialists, health technology assessment experts, or industry partners. Although the response rate in the online rounds was 40%, we consider that there was a wide representation covering all European countries and specialities involved. Additionally, study designs and endpoints presented in this Delphi study were derived from an extensive bibliometric literature analysis; some represented a diverse set of items, such as quality assurance endpoints or alternative study designs. To minimise misinterpretation, participants received clear definitions or examples in the survey or during discussions.

Although the project's objective (ie, to determine what constitutes meaningful benefit in order to inform clinical implementation and policy decisions, including reimbursement) was explicitly communicated, a potential limitation is a different interpretation by participants, focusing on feasibility and practical considerations of evidence generation, potentially affecting their voting decisions. The absence of the patient perspective is also an important limitation. The next phase of the VBRO project will ensure that appraisal of radiotherapy innovations is aligned with patient needs and priorities.

Finally, value-based appraisal requires balancing meaningful benefit with costs. Although the Health Economics in Radiation Oncology project has developed a time-driven activity-based costing model for radiotherapy, further analysis in the VBRO project will explore how insights from both projects can be integrated.[29,49]

Conclusion

To our knowledge, this Delphi study is the first to report a consensus within the radiation oncology professional community on the appropriate level of evidence and outcomes required to support clinical practice change or reimbursement for radiotherapy innovations. To summarise, for each of the four categories of radiotherapy innovations, a consensus was reached on a set of study designs and endpoints suitable for identifying high-value interventions and supporting their clinical adoption or policy decisions. Although RCT evidence remained a high priority, non-randomised high-quality evidence was also considered essential for specific indications or innovations, particularly where innovations are emerging or where technical aspects are important. Equally, the importance of a broader set of clinical endpoints beyond overall survival was acknowledged, including local control, functional endpoints, and operational endpoints. By defining this consensus, these results pave the way for a structured and radiotherapy-specific appraisal strategy that considers the innate complexity of radiotherapeutic treatment modalities. The ESTRO VBRO project will take this forward in the next steps of the project, using the range of accepted study designs and endpoints to develop an appraisal framework to support prioritisation of radiotherapy innovations, with the aim of improving policy decision-making on the dissemination of innovation and reimbursement in the framework of public health systems.

Contributors

All co-authors played an important role in interpreting results, revised the manuscript, and approved the final version. MV participated in conceptualisation, methodology, validation, formal analysis, investigation, writing the original draft and editing, and data visualisation. ML, MA, PB, and JMB participated in conceptualisation, formal analysis, investigation, and editing the draft. YL and AA participated in conceptualisation, methodology, data validation, formal analysis, investigation, writing and editing of the original draft, data visualisation, and supervision.

Declaration of interests

YL is former president of the European Society for Radiotherapy and Oncology (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; and receives financial support from Astra Zeneca for work unrelated to value-based radiation oncology research. MA acknowledges the support of the Engineering and Physical Research Council (grant number EP/T028017/1). All other authors declare no competing interests.

Acknowledgments

MV acknowledges the support of the value-based health-care 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.

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