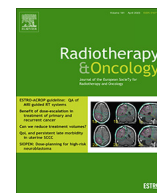




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Original Article

A systematic literature review of definitions and classification systems for radiotherapy innovation: A first step towards building a value-based assessment tool for radiation oncology



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ABSTRACT

Introduction: Timely access to radiotherapy innovations remains suboptimal, partly because there is no commonly agreed appraisal system suitable for the broad range of radiotherapy interventions. The Health Economics in Radiation Oncology (HERO) programme of ESTRO therefore engaged in building a radiotherapy-specific value-based framework. We report on a first step towards that aim, documenting the available definitions and classification systems for radiotherapy interventions.

Methods: A systematic literature search was carried out in Pubmed and Embase, following PRISMA methodology and using search terms on 'innovation', 'radiotherapy', 'definition' and 'classification'. Data were extracted from articles that met prespecified inclusion criteria.

Results: Out of 13,353 articles, 25 met the inclusion criteria, resulting in the identification of 7 definitions of innovation and 15 classification systems applicable to radiation oncology.

Iterative appraisal divided the classification systems into two groups. A first group of 11 systems categorized innovations according to the perceived magnitude of innovation, typically 'minor' versus 'major'. The remaining 4 systems categorised innovations according to radiotherapy-specific characteristics, such as the type of radiation equipment or radiobiological properties. Here, commonly used terms as 'technique' or 'treatment' were found to be used in different meanings.

Discussion: There is no widely accepted definition or classification system for radiotherapy innovations. The data however suggest that unique properties of radiotherapy interventions can be used to categorise innovations in radiation oncology. Still, there remains a need for clear terminology denoting radiotherapy-specific characteristics.

Conclusion: Building on this review, the ESTRO-HERO project will define what is required for a radiotherapy-specific value-based assessment tool.

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Innovation in healthcare can be a driver for improvement, through development of new treatments that meet unmet need, through optimising delivery of existing treatments and by strengthening the wider healthcare system. Nevertheless, innova-

tion can be regarded with suspicion, especially if its superiority to the current standard of care is not yet proven or if it comes at a significantly increased cost. Over the last twenty years, spending on cancer in Europe has significantly outpaced the rise in cancer incidence, reflecting the number of innovations. [1] The focus of this expenditure is mainly on pharmaceuticals, rising because of increased usage (increased number of patients, new drugs, new indications) as well as higher prices of new drugs. [2] In contrast, expenditure on and reimbursement of radiotherapy have clearly lagged behind: in Europe, only an average 7.8% of oncology budgets is dedicated to radiation oncology (RO) [1,3], despite many

Abbreviations: ESTRO, The European Society for Radiotherapy and Oncology; ESTRO-HERO, The European Society for Radiotherapy and Oncology Health Economics in Radiation Oncology project; RO, Radiation oncology.

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advancements leading to more effective or less toxic radiation treatments. [3].

Assessing the benefits of interventions in RO is more complex than appraising a new drug, as the types of innovation and mechanism of use are incredible diverse. For instance, innovations in RO encompass everything from new immobilization devices (e.g. masks) to radiation beams with different biological properties (e.g. protons), or novel methods of treatment delivery (e.g. FLASH radiotherapy). [4–6] Contrary to systemic therapies, innovations in RO often require specific training, necessitating a learning curve that may conceal benefit in earlier assessments. [4,5] Whilst the randomized controlled trial (RCT) is the gold standard method of evaluation for cancer drugs, the diversity of radiotherapy interventions requires a nuanced and intervention-specific approach to evidence generation and appraisal, that considers different types of evidence (e.g. observational data) and endpoints (e.g. organ preservation). [5,6].

For over a decade, the concept of ‘value’ has been proposed as a useful asset to evaluate the impact of a new intervention and support routine reimbursement in clinical practice. Value takes into account both the health outcomes (that matter most to patients) and the cost spent over the total cycle of care, meaning it can increase by either improving outcomes or reducing costs. [4,7] Several value-based evaluation tools have been developed for cancer care, but none of these (e.g. 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 blocksTM) are immediately transferable to locoregional cancer treatments, such as radiotherapy and oncological surgery. [5,8–10] The difficulties to obtain evidence of longer term benefit in some radiotherapy innovations, combined with high upfront capital or human investments just to even test a new innovation, create challenges to appraise benefit and value. For example, the fact that reducing late toxicity is expected to be the major benefit of proton beam therapy, along with the high costs associated with dedicated proton therapy facilities, has hampered its evidence generation. [11] Appraising potential benefit of RO innovations without considering these specificities, could delay reimbursement and implementation, hindering patients’ timely access to cure and care. Equally, a lack of an agreed system of appraisal for RO innovations has resulted in differential diffusion and adoption of low value interventions, which neither provide significant benefit over and above existing standards nor come at high cost. [4–6,12] Proton beam therapy, to take the same example, has demonstrated benefit for selected patients, but its higher cost may not be warranted for others, where a similar clinical benefit is not achieved. [11,13].

Therefore, a value-based scale specifically for radiotherapy interventions is required to justly assess innovations in RO [8]. Such a dedicated framework demands first a classification system that encompasses the broad range of innovations. [4–6,8,14] This paper reviews the literature for definitions and categorisations of innovations in RO and describes their use and properties.

Methodology

A systematic literature search was carried out on 15/02/22 in Pubmed and Embase, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline [15]. The search strategy included keywords and terms for ‘innovation’, ‘radiotherapy’, ‘definition’ and ‘classification’. The full

² ESMO-MCBS; ASCO Value framework; NCCN evidence blocksTM are value-based tools used in oncology to facilitate decision-making for clinicians and/or support value evaluations for healthcare policy makers.

search strategy is available in the [supplementary material](#) (Addendum I).

Study selection

Articles describing a definition and/or a classification system for innovations in or applicable to RO were included. Only articles published in English were included. A ‘definition’ was viewed as any explanation of the meaning of an innovation, whereas ‘classification’ was defined as any explanation of different categories of innovative interventions.

Articles were excluded if they did not have any application to RO, they did not contain a definition or classification system for innovations or were not written in English. In addition, surveys, abstracts, and conference proceedings were also excluded. No limitations for time period were used for selection of articles.

Abstract and titles retrieved from the literature search were screened for inclusion in full-text review. Full-text records were then evaluated against inclusion criteria. Selection of articles by full text was done by one author (MV), with a second reading to ensure consistency performed by two other authors (AA, YL). Any conflicts were resolved by consensus (2:1).

Data extraction

Data were extracted using a predefined data collection form formulated by three authors (AA, MV, YL). The definitions and classification systems with their characteristics and indicators were recorded as reported by the authors of each publication, as well as any relevant additional information. Uncertainties were resolved by consensus meetings with senior reviewers (AA, YL). The full framework can be found in Addendum II.

Categorisation of results

Characteristics of each categorisation systems were identified using the additional information that was extracted. Through iterative appraisal and consensus between authors (AA, MV, YL) it was decided to divide the systems into two groups, as discussed in Results.

Results

The initial search produced 13,353 articles. After a review of titles and abstracts, 119 articles were selected for full-text review. Of these, 24 articles were included in the analysis as they contained a definition and/or a classification system for innovation in RO. One additional article was identified through handsearch of the reference lists of selected articles, resulting in 25 articles for analysis. (See Addendum III for the PRISMA flow chart and addendum IV for the articles excluded by full text).

An overview of all selected articles can be found in [Table 1](#). Seventeen of the 25 articles published original definitions and/or classification systems. Five additional articles published original definitions and/or classification systems but also contained previously published definitions and/or classification systems from the seventeen originally identified. Three of 25 articles only contained previously published definitions and/or classification systems.

This review provides a narrative synthesis of the definitions and classification systems of innovation in RO. Any quantitative data or descriptors of definitions or categories, or additional information provided by the study authors to justify the categorisation of specific interventions into a system were also included. This additional information is referred to as the ‘indicator or descriptor’. For example, in the classification system by Swart et al., innovations are

Table 1

Overview of all publications, containing a definition and/or a classification system for innovation in radiotherapy. Note: Number of dots represents number of definitions or classification systems in a publication. Full dots represent the publication of a definition or classification system, not previously published. Empty dots represent a definition or classification system previously published, with reference to original publication in the right column.

Author	Year	Journal	Definition	Classification	Refers to
Berchuck	2008	Gynecol Oncol		●	
Halperin	2009	J Am Coll Radiol		●	
Zietman	2010	J Clin Oncol		●	
Fraass	2012	Semin Radiat Oncol		●	
Slavin	2012	Stereotact Funct Neurosurg	●		
Tombal	2012	Eur Urol		●	
Van Loon	2012	Lancet Oncol		●	
Zietman	2012	Semin Radiat Oncol		●	
Bortfeld	2013	Int J Radiat Oncol Biol Phys		●	
Jacobs	2015	J Hosp Adm		● ●	
Swisher-McClure	2015	Postgrad Med J	●		
Jacobs	2016	Br J Radiol	●	○ ○	Jacobs 2015
Jacobs	2016	Radiother Oncol		○	Jacobs 2015
Pomeraniec	2016	BMJ Innov		●	
Schnurman	2016	J Neurosurg		●	
Aapro	2017	Eur J Cancer	●		
Jacobs	2017	Br J Radiol		○	Jacobs 2015
Jeon	2019	J Health Econ	●		
Lievens	2019	Lancet Oncol		●	
Yu	2019	Med Phys	●		
Sansourekidou	2020	BJR Open		○	Jacobs 2015
Lievens	2021	Radiother Oncol		○ ●	Lievens 2019
Borras	2021	Radiother Oncol /Eur J Surg Oncol		○ ○	Lievens 2019
Swart	2021	Br J Radiol	○	○ ●	Jacobs 2015
Thijssen	2021	J Health Organ Manag	●	○ ○	Jacobs 2015

defined as “small, medium or large” according to the “number of staff needed”, which is a quantitative descriptor for classification. [16].

Out of the 25 selected articles, 7 original definitions of innovation were retrieved [17–23] (Table 2).

Five out of 7 definitions mention a specific type of innovation (disruptive innovation in three publications [20,21,23], radical innovation in one article [22]), or an innovation applied in a specific context (breast or prostate cancer, both in one article [19]). The other two publications give a definition for ‘innovation’, without mentioning any specification. [17,18].

Whereas 2 of the 7 definitions specify the effect of the innovation as a benefit or difference for patients [17,18], the others refer to impact in diverse ways: as impact on markets [21,22] or delivery of treatment [23], or simply as ‘cheaper and safer’ [20]. The definition by Jeon and Pohl uses multiple variables such as number of patents expressing innovation, demonstrating their effect in a mathematical model. [19].

Table 2
Definitions.

Author	Year	Type of innovation	Definition
Slavin	2012	Disruptive innovation	Comparable in terms of effectiveness but cheaper in terms of cost and safer in terms of morbidity
Swisher-McClure	2015	Disruptive innovation	Technological innovations that transform current markets and quickly replace existing technology
Jacobs	2016	No specific type	The intentional introduction and application within a role, group or organisation of ideas, processes, products or procedures new to the relevant unit of adoption, designed to significantly benefit the individual, group or wider society
<i>Swart</i>	<i>2021</i>		
Aapro	2017	No specific type	Any intervention within the care pathway that makes a meaningful difference to patients
Jeon	2019	Innovation in breast and prostate cancer only	<ul style="list-style-type: none"> • Innovation, measured as the number of approved drugs and the patent index five years before the cancer diagnosis • Innovation as measured by the cumulative patent index • Innovation as measured by the number of all cancer drugs
Yu	2019	Disruptive innovation	Revolutionary technology that fundamentally changes how we deliver radiation treatments, regardless if it causes the displacement of the market leaders in the industry or not.
Thijssen	2021	Radical innovation	Creating dramatic change in technology, processes, products and/or services that considerably transforms existing markets and industries, or even gives rise to new ones

Authors indicated in **bold** represent the publication of a definition, not previously published. Authors indicated in *italic* represent a definition previously published.

Table 3
Classification systems based on an expression of magnitude of innovation.

Basis for classification								
(expected) impact on patient	Differences with standard practice	Resources required	Training of staff required	Impact on business model				
○	●	○	●	○	Berchuck 2008	continuous change: upgrading of existing practices and generally does not require extensive new learning or changes	discontinuous change: advances require dramatic changes in practice	
○	●	○	○	○	Halperin 2009	extension of existing technology	new technology: sufficiently different from existing technology	
○	●	○	○	○	Zietman 2010	technology evolution: steady incremental development and improvement of existing, already transferred, technology	technology transfer: adoption of new technology that involves novel and untried aspects.	
○	●	○	○	○	Fraass 2012	technological improvements: can be technical better but do the same thing	new treatment strategies: different clinical treatment, need to be evaluated with clinical studies	
○	●	○	○	○	Tombal 2012	continuous improvements: leads to slow progress, if not stagnation	true (breakthrough) innovation: change our approach to disease	
●	●	●	○	○	Bortfeld 2013	Incremental improvements: often “trumped up” and touted to have greater impact than they do. Can merely represent repackaging of previously available technologies	real improvements: hard to come by; really good ideas can be elusive, costly, and require meaningful engineering/technological changes	
○	●	○	●	○	Jacobs 2015	incremental innovation: introduces alterations to existing treatments, technologies, methods or systems that lead to improvements in content or efficiency. They are mostly linear and continuous in character.	radical innovation: those treatments, technologies, and markets and organisational changes that are completely new to the clinic. Such major innovations require skills, abilities and knowledge different from those required to master the old technologies. These are non-linear, resulting in a discontinuation of the existing line.	
○	○	○	○	●	Pomeranic 2016	sustaining innovations: reaffirming current paradigms of competition and technological progression	disruptive innovation: transforming existing paradigms and shifting them towards new dimension of innovative performance.	
●	●	○	○	○	Schnurman 2016	refining period: new developments merely improve the existing method with relatively modest clinical impact	expanding period: a significant innovation spurs rapid change that considerably alters patient care	
●	●	○	○	○	Lievens 2019	incremental innovations: innovations involve less obvious changes in clinical practice, which are continuously implemented in radiation oncology or cancer surgery.	stepwise innovations: new interventions potentially improving outcome in a stepwise fashion; those that change clinical practice in a significant way for patients and physicians.	
○	○	●	○	○	Swart 2021	Small innovation: 0-0,5 FTE or 800h budgeted 1 discipline needed 1-2 project members needed	Medium innovation: 0,5-1,0 FTE or max 1600h budgeted 2-3 discipline needed 3-4 project members needed	Large innovation: >1 FTE or >1600h budgeted >3 discipline needed >4 project members needed

A full dot indicates on what basis the different categories are defined. Different aspects were identified, based on information extracted from the selected publications, and can be found in the first columns. The following aspects for categorisation are indicated: (expected) impact on the patient; difference or comparison with a standard of care or standard practice; capital or human resources required; training or additional skills of staff required; expected impact on business model such as competition [5,15,24-28,30-32,34].

is based on the (expected) impact on the patient, described as patient outcomes or clinical impact [32], or not further specified [30]. The difference in magnitude of innovation can also be based on resources required [30,33], such as the ‘small, medium or large’ innovations as described by Swart et al. These are determined by quantitative descriptors: number of hours of staff time budgeted for the project, number of disciplines involved and number of project members needed. [16] Other authors use difference with current standard of care or clinical practice [5,25-28,32,34] to express the difference in magnitude. For example: the ‘technology transfer’ as described by Zietman et al., meaning the adoption of new technology that involves novel and untried aspects. [26] Another way to express the difference in magnitude of innovation is the difference in training or skills needed [24,34]. Berchuk et al. for example describe ‘continuous change’ as practices that do not require extensive new learning. [24] Lastly, there is one system based on (impact on) the business model, described by Pomeranic et al. This system discerns between sustaining or disruptive innovations, where the latter transforms existing paradigms of competition. [31].

Four out of 15 classification systems categorise innovations based on radiotherapy-specific characteristics, such as the type of radiation equipment, mode of delivery, or radiobiological property of the intervention. [4,14,29,34] (see Table 4).

The classification by Van Loon et al. has only two categories, defining innovations as a technique or technology. [29] Technique refers to a different dose, fractionation schedule, or target volume, for example the omission of elective nodal irradiation. A technology refers to a new treatment modality or an important technical

modification, such as proton-based particle therapy. There are no quantitative descriptors for the categories provided by the authors.

The system proposed by Zietman et al., describes three groups: technical, dosimetric or biological innovations. [14] (ref). This classification is a way to judge innovative concepts in radiotherapy, and to determine their need for testing and evidence. Technical innovations are systems or devices that improve the targeting of radiation beams or that may speed the delivery and convenience of radiation delivery, e.g. volumetric-modulated arc therapy or high-dose rate brachytherapy. Dosimetric innovations allow for the safer delivery of higher doses through greater accuracy and better sparing of more normal tissue, for example IMRT (intensity modulated radiotherapy). The last category is biological innovations, potentially bringing unique biology to the clinic, e.g. proton-therapy. The authors propose measurable descriptors for only two out of three categories: such as speed of delivery for technical innovations, or dose-volume histograms for dosimetric innovations.

The classification system used by Jacobs. et al. adapted the definition of the four categories for innovation from the ‘OSLO manual classification’, published by the OECD and Eurostat, to interventions in RO. [34,35] The categories are product (or treatment), technological, market and organisational innovations, and their radiotherapy-specific description can be found in Table 4. A product (or treatment) innovation is described as a new or significantly improved treatment, in terms of its characteristics or intended use, e.g. IMRT. Technological innovation is based mainly on equipment and devices, for example an MR-Linac. Market innovation is defined as the entry of the innovation into a new hospital

Table 4
Classification based on radiation oncology characteristics.

Van Loon 2012	Technique: refers to a different dose, fractionation schedule, or target volume	Technology: refers to a new treatment modality or an important technical modification		
Zietman 2012	Technical: these are systems or devices that improve the targeting of radiation beams or that may speed the delivery and convenience of radiation delivery	Dosimetric: many systems theoretically allow for the safer delivery of high doses of radiation through greater accuracy and the exclusion of more normal tissue from the high- and low-dose volumes. The dose volume histogram has become the comparator by which these devices are judged.	Biological: some radiation therapies potentially bring unique biology to the clinic.	
Jacobs 2016	Product (treatment): The introduction of treatments that are new or which constitute a significant improvement in terms of their characteristics or intended use	Technological: The introduction of new or significantly improved technological processes or methods that have no noticeable consequences for the patient. This also includes new equipment or devices	Market: The entry into a hospital area in which the clinic has not operated before	Organisational: The introduction of new or significantly improved forms of organizational structure, management methods and systems aimed at improving the use of knowledge, the quality of services or the efficiency of the workflow
Lievens 2021	Technologies: new types of equipment or devices for cancer treatment	Technique: referring to new ways of using technology	Treatments: new ways of care delivery for specific indications, all or not as a consequence of the availability of novel techniques and/or technologies; also organizational changes	

Note: Order of categories is the same as order of categories as published by authors.

area or for a new health care indication in which the hospital has not operated before, e.g. a combination of radiotherapy and systemic therapy, attracting new patients, or starting a new outpatient clinic. Lastly, organisational innovations are about the structure, management methods or workflows of an organisation, e.g. introduction of an electronic health record.

The classification proposed by Lievens et al. divides radiotherapy interventions into three categories: technologies, techniques and treatments. [4]. Technologies refer to radiotherapy-specific equipment or devices, such as linear accelerators; techniques are seen as new applications of these devices, e.g. adaptive radiotherapy. Lastly, treatment innovation refers to new ways of care delivery for specific indications, all or not as a consequence of the availability of new technologies or techniques, such as hypofractionated schedules. The authors do not provide measurable or quantitative indicators for these categories.

Interestingly, two out of four RO specific classification systems are combined with a second classification system. The RO specific classification in technologies, techniques and treatments proposed by Lievens et al., is combined with a categorisation in incremental or stepwise innovations. [4,8] Similarly, the RO specific classification in product, technology, market or organisational innovations, proposed by Jacobs et al., is combined with incremental and radical innovations by Jacobs et al., or combined with small, medium or large innovations as proposed by Swart et al. [33,34].

Discussion

The concept of value can be used to support timely access to radiotherapy innovation for patients, but radiotherapy interventions require a dedicated value-based framework.[5,8–10,36] This review takes the first step towards building a RO-specific tool, by searching existing definitions and classification systems for innovations in RO. [4].

Seven different definitions of innovation, used in RO, were found in the literature. No widely accepted or consensus definition

was found, but some definitions are published multiple times by different authors. More importantly perhaps, many definitions lack precision, which increases their flexibility but also can make it challenging to define whether an intervention can be considered “innovative”.

The classification systems found in the literature were grouped in one of two approaches by the reviewers. The first classification considered the magnitude of innovation, expressed in different ways, and the second sought to differentiate radiotherapy innovation according to its unique characteristics, such as its mechanism of delivery, biological properties or outcome delivered.

Across the different categorisation systems developed focusing on properties of radiotherapy innovation there were some similarities, for example classifying according to common technological aspects of RO, [4,14,18,25,26,29] or radiobiological properties [14,29].

However, despite these recurring characteristics, there is a lack of consensus in terminology. For example, common terms such as ‘treatment’ or ‘technique’ are used frequently, yet each time with a different meaning. Going forward, general agreement on the definition and terminology of these recurring characteristics and commonly used terms will be addressed in the next steps of the project, to rule out the existing ambiguity.

Similar to the definitions, most classification systems leave room for interpretation and only few provide quantitative descriptors, which could impact on its reproducibility. Consensus is important and strict definitions or measurable descriptors can support this. Equally, being more prescriptive can result in many innovations failing to be classified adequately. Combining more than one system may offer an alternative, allowing for a more specific categorisation without too strictly defined categories. [4,8,33].

A value-based tool should also consider the diversity in outcomes and their relevance for the different interventions. In some innovations we expect a clinical benefit, such as proton beam therapy, where others are intended to improve workflow and efficiency, e.g. AI-based autocontouring. [5,8,37] Whether an intervention results in a change in a clinical outcome or if its

impact has a more indirect relation with the patient, is also a consideration which may help to support classification.

A categorisation system in a value-based assessment tool should help prioritise which endpoints need to be collected and measured, to support implementation or reimbursement for different types of interventions. Patient-centered outcomes are crucial in this: current value frameworks have not – or not sufficiently – accounted for the patient perspective in selecting relevant outcomes. [5,8,37] In addition, alternative approaches to evidence generation or trial design, such as real-world evidence data, can be used as a pragmatic compromise for evaluating the benefit of selected innovations. [4,6,8].

There are some limitations in this review that should be acknowledged. Firstly, the terminology used in publications to describe ‘innovation’ is variable. To capture all relevant literature, the search strategy (see Addendum) included alternative terms and synonyms. Furthermore, due to the often-narrative nature of most publications on innovation, ‘risk of bias assessment’ was not performed for the articles included in this review. Only a few of them are the result of evidence-based research or consensus building. In some of the selected publications, there was only a limited amount of information on the definition or classification system. It is possible that the interpretations in this article, despite consensus, deviate from the intended meaning by the original authors. In contrast, three authors of this article were (co-) author in publications selected in this literature review. The involvement of other experts in the field was therefore searched to guarantee unbiased processing of the results.

Conclusion

This literature review shows there is no widely accepted definition nor a preferred classification system used for innovations in radiotherapy. Overall, two major approaches were found to categorize innovations, suggesting that key characteristics of radiotherapy interventions exist and can be used to categorise innovations.

Building on this literature review, the ESTRO-HERO project will assess the suitability of the existing classification systems and define what is required for a categorisation of innovations in a value-based healthcare context for RO. Important aspects, unique to RO, will have to be considered: the diversity of innovations, the learning curve and user-dependency, the impact of an innovation on multiple steps in the care-path, can all influence the assessment of value of new radiotherapy interventions.

Subsequent steps in the ESTRO-HERO project will be dedicated to outcomes, evidence and benefit of innovative interventions. These key components will eventually be assembled to create a value-based framework dedicated to radiotherapy interventions, facilitating timely and early access for patients to innovations that provide clinical or societal benefit. [4].

Declarations of interest

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YL is former president of ESTRO, co-chair of the ESTRO-HERO project and promotor of the Ugent Chair on ESTRO value-based health care, which is financially supported by the ESTRO Cancer Foundation. She receives financial support from Astra Zeneca, for work unrelated to the VBHC research.

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ML, PB, JB, AA have no conflicts of interest to declare.

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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.radonc.2023.109602>.

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