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COMMENTARY

Access to innovative radiotherapy: how to make it happen from an economic perspective?

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Introduction

Due to the demographic evolution, both incidence and prevalence of cancer are increasing in most parts of Europe. Whereas elderly patients have classically been perceived less amenable to undergo aggressive cancer therapy, the current rapid evolution towards more effective and better-tolerated cancer treatments is changing this. But there is no free lunch: more patients being treated more intensively with more advanced technologies inevitably has its cost. Health expenditure on cancer increased from €35.7 billion in 1995 to €83.2 billion in 2014, one of the major reasons being the ever-growing budget of cancer drugs, amounting to over €19 billion in 2014 [1].

In addition, the rapid diffusion of new technologies has been proposed as a major cause of increasing healthcare costs [2]. Radiation oncology, a high-tech discipline in continuous evolution through a combination of new treatment schedules, more advanced techniques and novel technologies, does not remain spared of these increasing financial demands. Although one should not overlook the dedicated human resources needed to deliver up-to-date radiotherapy [3], it is specifically the increasingly sophisticated radiotherapy equipment that is scrutinised from an economical perspective.

Many new techniques, such as adaptive or stereotactic body radiotherapy (SBRT), only to name a few, have rapidly gained acceptance and are already widely established in daily practice. At least, insofar reimbursement has made this possible: it is well-known that insufficient financing delays the implementation of health innovations [4]. Similarly, the introduction of cutting-edge technologies, such as particle therapy, is also triggering a lot of discussion on whether the expected clinical benefit justifies the higher investment and operating costs, hence reimbursement. Regardless of this ongoing debate, the overall cost consequences of clinical, technical and technological evolutions in radiotherapy have so far remained largely unexplored.

One of the reasons for this apparent lack of evidence on the economical aspects of radiotherapy, in vivid contrast to the abundant literature available for oncology drugs, can be brought back to the different path and timeline to bring drugs and devices onto the market [5]. As neither comparative effectiveness nor economic evidence is mandatory before market launch, the – post-hoc – evidence generation is typically shifted to the responsibility of the healthcare providers, after investments have been made. In many cases, this delays correct financing, which again hampers evidence generation [6].

With the specific context of radiation oncology in mind, this article will discuss health technology assessment (HTA), economic evaluation and evidence generation, and suggest a financing approach that has the potential to break the vicious circle between lack of evidence and lack of financing.

Health technology assessment: the broader picture

In view of implementation, a new treatment or technology must not only outperform the available standards of care in terms of clinical outcome, but also generate benefits from a broad societal perspective. Whereas economic evaluations have become the mainstay to prove the value for money of new healthcare interventions, they represent only part of the entire HTA process. In order to support policy makers, payers and government agencies in making evidence-based decisions about the introduction and appropriate use of these interventions, and to inform providers and patients, evaluation of the broader context is needed.

HTA builds on clinical evidence and encompasses a comprehensive multidisciplinary process that evaluates the social, economic, organizational and ethical issues related to a health intervention or technology. It addresses five different questions [7]: (1) Can a healthcare intervention achieve its expected goal when used in optimal circumstances? (Efficacy); (2) Does the intervention do more good than harm when used in routine practice? (Effectiveness); (3) What is the balance between the health outcome obtained and the resources required? (Efficiency or Cost-Effectiveness); (4) Is the supply of services matched to locations where they are accessible to persons that need them? (Availability) and (5) Who gains and who loses by choosing to allocate resources to one healthcare program instead of another? (Distribution). By doing so, it centres on accessibility, affordability and equity, all of which have been found to relate to survival [8].

Clinical research focuses on answering the first question, but falls short in addressing the question whether or how the new intervention performs in a real-life environment. It is

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primarily dedicated to testing the potential of innovative treatments and technologies in improving outcome of specific patient populations, that is, in improving the achievable outcome. But what is actually achieved in daily practice not only depends on what would be achievable with optimal care, but also on how well we succeed in delivering this optimal care to all patients who may benefit. Health services research addresses the remaining questions. It describes how health systems work, how they may go wrong and how health system performance can be optimized with the aim to improve outcomes [9]. In order to realize the full impact of novel treatments and innovative technologies, translation of clinical evidence into the healthcare system is key and requires alignment of research over the entire spectrum from basic over translational and clinical into health services research.

Three dimensions characterize health system performance: accessibility, quality and efficiency.

Accessibility defines the extent to which patients are able to get the care they need, when they need it. As demonstrated in the ESTRO-HERO project, 3 out of 10 patients do not make it to the indicated radiotherapy and a large variation in available high-tech radiotherapy equipment is documented, even in a high-income region as Europe [10–13]. Not surprisingly, the picture is even grimmer in many other parts of the world [14].

Quality focuses on whether the right – evidence-based – care is delivered in the right way. We are, unfortunately, not short of examples in radiation oncology that demonstrate the lag time between evidence generation and uptake in daily care. One striking illustration is the (lack of) adoption of hypofractionated radiotherapy in breast-conserving treatment. Whereas large randomised trials have proven the equivalence of shorter and more patient-convenient fractionation schedules and guidelines have endorsed this, the actual uptake remains limited and highly variable across the world [15–18]. In contrast, whether novel radiotherapy approaches are also safely introduced in routine practice, following current quality-assurance standards, is not well-documented.

Efficiency, the third dimension of health system performance, introduces costs into the picture: it evaluates whether accessibility and effectiveness are optimized in relation to the resources expended, that is, the costs incurred.

How to pursue value for money?

Efficiency measures whether we are getting the best value for money from the available healthcare resources. Available resources are always limited, even in high-income settings. As a consequence, the decision on which new healthcare interventions to adopt in routine practice inherently needs to rely on a trade-off between the costs and the expected benefits. This is classically performed through economic evaluations, where the extra cost of a new intervention (compared to the standard treatment) is balanced to the additional gain in clinical effect. The type of effects defines the type of economic evaluation. Most frequent are cost-effectiveness analyses (CEAs), where the outcome is expressed as a clinical effect, e.g., survival, and cost-utility analyses, in which quality-adjusted life-years incorporate the quality into the years of life gained. The result is summarized in the so-called incremental cost-effectiveness ratio (ICER) that allows benchmarking the intervention under consideration to the willingness-to-pay of the society in which it is evaluated [19].

Although economic evidence has become mandatory to support healthcare decision-making regarding new therapeutic interventions, challenges remain in generating high-quality cost and cost-effectiveness data. This is especially the case for complex and rapidly evolving treatment modalities such as radiotherapy, where therapeutic benefits may only become apparent after many years. Two literature reviews on available cost-effectiveness studies demonstrated that there remains a lack of up-to-date, robust and qualitative economic evidence in radiotherapy [20,21]. In addition, radiotherapy costs, the first necessary step towards cost-effectiveness, investment and reimbursement setting, are an often-underestimated component of the economic assessment of new radiotherapy interventions. Only just over 50 publications have documented cost calculation in photon radiotherapy since the eighties. In addition to their limited number, the real treatment costs are difficult to derive from these data, due to the large heterogeneity in scope, inputs and outputs, and to the infrequent use of conventional costing methodologies [5,22].

Economic evaluations define if a new intervention is economically acceptable for society, however, do not guarantee its affordability, that is, whether society has the budgets to implement and reimburse it. This is critically dependent of the total healthcare budget, and on how much of that total budget is directed to cancer care, respectively, radiotherapy. To address affordability along with acceptability, there is growing recognition that a comprehensive economic assessment of new healthcare interventions requires both cost-effectiveness and budget impact analyses (BIAs) [23,24]. One major difference between CEA and BIA is the target population: though in both cases, consistent with the reimbursement request, it is closed in CEA and open in BIA. This means that in addition to knowledge of the actual size of the target population conform the inclusion criteria of the trial generating the evidence, one should also forecast its evolution over time.

There may be various reasons why a target population evolves with time, as can be illustrated for SBRT for oligometastatic disease. The fact that new imaging modalities increase detection of this early metastatic disease state, along with SBRT being very well tolerated – clinically as well as in terms of practical burden – stimulates uptake in routine practice. From a societal perspective, the decision whether or not to reimburse this indication is however not straightforward: while clinical data are accumulating, level 1 evidence is still lacking and data on the actual cost and cost-effectiveness are equally sparse [25]. In this quickly evolving field, indications have evolved towards the acceptance of a growing number of oligometastatic sites per patient and a broader selection of patients, also the elderly and those with comorbidity. Lastly, novel drugs may induce more chronic disease states, which may require additional local ablative treatment

to lesions that become less responsive to systemic treatment. Seeing all these factors, it is extremely difficult to forecast the target population and SBRT needs in the years to come, let aside the expected impact on the radiotherapy budget.

While CEA and BIA have been widely adopted for drugs, these methodologies have turned out more complex to undertake for technologies. In radiotherapy, the clinical benefits following introduction of new treatments, techniques or technologies are often incremental in nature and may take long time to mature. Also, new radiotherapy approaches tend to be more costly during the implementation and learning phase [25,26]. These uncertainties inherently related to the gradual process of radiotherapy evolution, influencing outcome as well as costs, make CEA and BIA more difficult to accomplish. Moreover, in contrast to drugs, which typically undergo the entire cycle of comparative effectiveness and economic evaluation prior to market introduction and reimbursement, new radiotherapy devices do not need efficacy trials before market launch. As a consequence, the burden of clinical and economic evaluation typically falls on the radiotherapy professionals, and imposes them with the financial risk of investment and often delayed reimbursement [5].

These unique characteristics of technology uptake, approval and reimbursement of treatments delivered with new devices, contribute to a knowledge gap in our understanding of the value of new technologies [6]. Following the increasing attention for the value of new cancer drugs, value-based healthcare is finding its way to radiation oncology. Value is defined as outcomes relative to costs, hence also relates to efficiency, yet avoids the negative connotation of cost-reduction often perceived with cost-effectiveness. Core to the value-based approach is maximizing value for the patients, that is, achieving their best outcomes at the lowest cost. Outcomes are defined condition-specific and multidimensional, should address what matters to the patient and align to the patient's sense of value. The cost, conversely, refers to the total costs of the full cycle of care for the patient's medical condition, not the cost of individual services. It is expected that the development of value-based frameworks in radiation oncology will stimulate standardization of structures and processes and will reduce variation in care, with the ultimate expectation to encourage high quality and access. We are just at the onset of this development, which will require a rethinking of how to consider and carefully monitor processes, costs and outcomes [27,28].

Evidence generation from an economic perspective

Although it is well recognized that comparative effectiveness is critical for supporting the appropriate use of new interventions, generating such data in radiotherapy remains challenging.

Randomized clinical trials (RCT) are still regarded as the "gold standard" for comparative data generation [29]. An economic analysis embedded into a clinical trial is known as piggyback analysis. Here, additional economic cost and outcome data are collected and analysed to serve the economic question, whereas the trial itself is designed to respond the clinical question. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) published recommendations on how to conduct such trials [30]. Apart from considerations regarding the actual analysis, they also stress the importance of full follow-up data reflecting effectiveness rather than efficacy, of direct endpoint measures and of utilities obtained directly from the study population. It is moreover obvious that all resources that may influence overall costs be collected. Possible advantages of incorporating economic data collection into an otherwise clinical trial are the rigorous experimental design, the availability of patient-level data and of infrastructure and processes for prospective data collection [31]. But there are also challenges, related to the methodology, the data collection, the valuation of the resources. There is no one standard approach to be recommended; rather, the most optimal approach is to be defined for each individual trial [31].

More importantly, RCT characteristics are frequently inconsistent with the key criteria for evidence-based decision-making: they lack external validity [32]. In radiotherapy, there may be a multiplicity of treatment approaches – all or not in combination with systemic therapy, various fractionation schedules – and technical modalities available by indication, which are hard to capture in one study. Moreover, more advanced radiotherapy frequently only translates into improved outcome after many years, when local control starts to impact survival, or, more typically, when decreased late toxicity improves quality-of-life. RCTs in radiotherapy therefore either report intermediary endpoints, or take a long time to mature. Too long: by the time the trial is concluded, the data may have become obsolete due to changed treatment strategies and radiotherapy technology or to shifts in patient populations and indications.

The methodological solution applied to overcome these limitations is modelling. From an economic perspective, incorporating additional assumptions and sensitivity analyses allows comparing more relevant treatment options and incorporating evidence from other trials and data sources, translating intermediate endpoints into final consequences, extrapolating shorter into longer time horizons, generalizing to other settings or populations [19,33]. Specifically for radiotherapy, dose-response models can be used to predict the potential clinical benefit of new techniques and technologies [34]. The Dutch scientific and healthcare governance bodies have accepted such a model-based approach for the generation of relevant evidence for new technologies in healthcare. Based on predicted severe normal tissue complication probabilities (NTCPs), patients are allocated to standard care (e.g., intensity modulated radiotherapy) or to the experimental therapy (e.g., proton beam therapy, PBT), while patients in whom the dosimetric data predict equipoise could be enrolled in a RCT [35–37]. In head and neck cancer, a CEA was performed on this approach using NTCPs as predictive markers: whereas PBT was not cost-effective in all patients, it was when applied to an enriched patient population baring the highest risk of toxicity [38]. But whatever modelling applied, the resulting economic evaluations will unavoidably

remain an assortment of assumptions that remains to be validated. Hence, to facilitate the best decision-making for society, we need to evolve from efficacy, proven in well-selected patients treated in well-controlled and research-dedicated settings, to effectiveness in 'real patients' with 'real resource use'.

One approach could be to surpass the dichotomy between clinical and real-life data and to embrace blended evidence generation [39,40]. An ISPOR task force investigated the collection of real-life data and described it as "everything that goes beyond what is normally collected in phase III clinical trials in terms of efficacy" [41]. As such, real-life evidence can take many forms, observational data from cohort studies, patient registries, administrative data or healthcare claims and costs, only to name a few. In the context of economic evaluations, real-life data provide better insight into effectiveness, give additional information to data from randomised trials, support health economists to better manage uncertainty when making reimbursement decisions and validate the effectiveness after launch of the new intervention. Although such data bare the risk of lower quality, missing data or poorly specified information and may be more difficult to collect prospectively [42], in a continuum of blended evidence generation, real-life data could provide the multifaceted, practice-oriented approach to clinical effectiveness research, complementing the other data sources [39]. As an example, the European Organisation for Research and Treatment of Cancer has embraced this idea of new continuity solutions from proof of concept to pragmatic trials evaluating effectiveness and efficiency, based on real-world outcome, quality of life, resource utilisation and cost data [43].

Leveraging innovative reimbursement strategies

The broad collection of clinical and economic outcome data does not belong to common practice (yet), but could, amongst others, be fostered by the introduction of new reimbursement strategies. If it is inappropriate to solely rely on clinical trials to capture the typically incremental evolution in radiotherapy, the same can be argued for the reimbursement system employed. In a context of uncertainty, healthcare payers are increasingly looking into innovative reimbursement approaches matching the request for rapid patient access to potentially beneficial health technologies with the requirements to ensure acceptability and affordability. These can take many forms, depending on the goal pursued, be it managing budget impact, managing uncertainty related to clinical and/or cost-effectiveness or managing utilization to optimize performance. The HTA Policy Forum grouped these different approaches under 'managed entry agreements or MEAs', defined as "an arrangement between a manufacturer and payer/provider that enables access to (coverage or reimbursement of) a health technology subject to specific conditions" [44,45].

Financing systems that focus on the broader generation of clinical and/or cost-effectiveness evidence are referred to as 'coverage with evidence development (CED)'. CED allows provisional access to promising technologies earlier in their life cycle when evidence is still uncertain, by making the coverage decision conditional upon targeted research or the collection of additional population-level evidence [40,46,47]. Aligning reimbursement to evaluative evidence generation may help to overcome the economic development trap in which the delay – or denial – to finance new interventions threatens evidence generation for or against these very interventions. In addition, it may justify appropriate adoption, or de-adoption, of new interventions or technologies using a value-oriented framework [6]. These advantages have to be balanced against the potential disadvantages of a higher burden of monitoring, data collection and analysis along with the risk of exposing patients, providers and society to treatments and technologies that may ultimately prove ineffective [46].

In 2011, the Belgian healthcare authorities denied reimbursement for SBRT, seeing the remaining uncertainty regarding its effectiveness, cost, efficiency and budgetary impact in Belgium. Yet, awaiting more (randomized) evidence, the Belgian obligatory health insurance initiated a CED project for innovative radiotherapy, including SBRT, where provisional financing was determined by real-life costs. In return, radiotherapy professionals committed themselves to evidence generation in collaboration with the Belgian cancer registry. This project not only aims to evaluate the Belgian patterns of care in SBRT, but also to generate real-life evidence to support ulterior uptake into the formal reimbursement system [25,26]. New technologies, such as particle therapy, are also amenable to such framework. The decision to grant financing of PBT in the Netherlands using a modelled-based approach is one example [35–37,48]. Acknowledging that the diffusion of PBT is threatened by scarce comparative evidence, Bekelman and Hahn even take it one step further by proposing reference pricing (RP) with evidence development to safeguard its sustainability. The current high price of PBT in the US is untenable for payers and patients and hampers evidence development. RP, on the contrary, providing a common level of payment for different therapies with similar outcomes for a specific indication, would preserve access to PBT while reducing financial barriers to evidence development, be it in the context of RCTs or observational cohort studies [49].

In conclusion, radiation oncology is a high-tech and quickly evolving discipline, with a plethora of new treatment approaches, techniques and technologies that progress more gradually than stepwise. If we want to tap the full potential of these promising innovations and assure that our patients get swifter access to high-quality radiotherapy, while avoiding unacceptable impact on the healthcare budgets under pressure, we have to accept new means of developing clinical and economic evidence. Using a blended approach to evidence generation, with modelling and real-life data supplementing more traditional methods, and adopting innovative reimbursement systems, closely aligned to data capture, are the way forward.

Disclosure statement

No potential conflict of interest was reported by the authors.

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