Towards an evidence-informed value scale for surgical and radiation oncology: a multi-stakeholder perspective

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Surgery and radiotherapy, two locoregional cancer treatments, are essential to help improve cancer outcomes, control, and palliation. The continued evolution in treatment processes, techniques, and technologies—often at substantially increased costs—demands for direction on outcomes that are most valued by patients, and the evidence that is required before clinical adoption of these practices. Three recently introduced frameworks—the European Society for Medical Oncology Magnitude of Clinical Benefit Scale, the American Society of Clinical Oncology Value Framework, and the National Comprehensive Cancer Network Blocks—which all help define the value of oncology treatments, were appraised with a focus on their methods and definition of patient benefit. In this Review, we investigate the applicability of these frameworks to surgical and radiotherapy innovations. Findings show that these frameworks are not immediately transferable to locoregional cancer treatments. Moreover, the lack of emphasis on patient perspective and the reliance on traditional, trial-based endpoints such as survival, disease-free survival, and safety, calls for a new framework that includes real-world evidence with focus on the whole spectrum of patient-centred endpoints. Such an evidence-informed value scale would safeguard against the proliferation of low-value innovation while simultaneously increasing access to treatments that show significant improvements in the outcomes of cancer care.

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Introduction

Across Europe, cancer care expenditures continue to rise exponentially, driven by the demographic transition of a growing ageing population, numerous therapeutic advances, and expanding choice and consumerism in health care.[1,2] In any health-care system it is essential that patients have access to therapies most likely to deliver tangible and sustainable improvements in outcome, whether it is survival, quality of life, reduced toxicity, the ability to return to work, or the ability to maintain a patient's prediagnosis level of activity. Additionally, health-care investment should obtain the highest level of health for the entire society. Yet, the increasing costs of cancer care do not de facto translate into overall improvements in health outcomes, partly because of substantial expenditures of new treatments that are of uncertain benefit.[3–7]

Harvard Business School professor, Micheal Porter, proposed[8] that to achieve value-based health care, the focus should be on increasing value for patients, in other words, increasing health outcomes that matter to patients, per dollar spent. However, understanding the true benefits of new treatment modalities remains a challenge because benefits are measured from a clinical trial perspective (eg, survival and progression-free survival) and there is little understanding of how a patient values these outcomes and how their disease and background influence the perceived value of these outcomes. In this context, the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) developed evidence-informed value frameworks that provide guidance on the likely benefits of newly approved cancer medicines.[9–12] Similarly, the National Comprehensive Cancer Network (NCCN) in the USA developed the NCCN Evidence Blocks, a tool that visually represents five key measures on the value of cancer treatments delivered in accordance with NCCN guidelines.[13] These frameworks mainly focus on categorising clinically meaningful benefits of new treatments to help inform decision making. Conversely, organisations such as the International Consortium for Health Outcomes Measurement (ICHOM) define how to capture, in a standardised way, the diverse range of benefits that long-established or new interventions might offer to patients throughout their entire disease history.[14]

Radiotherapy and surgery are locoregional cancer treatments that are key to multidisciplinary cancer care, whether they are used to improve survival, for tumour control, or palliation.[15–18] Whilst half of all patients with cancer have an indication for radiotherapy, up to 80% of patients will need one or more surgical intervention.[15,16,18,19] Inspite of this, these interventions have largely remained outside the scope of value frameworks because the evolution of these innovations and their financing mechanisms, and thus market access, are different. Before market introduction, new technologies only need to show safety[20] and although health technology assessments (HTA) become a prerequisite for reimbursement in some countries, these HTA processes still lag behind those required for systemic therapies.[21–26] Neither the concept nor the methods on how to address HTA for technologies has been accepted at a European level.[27,28] Furthermore, although there are excellent examples of randomised controlled trials (RCTs) in surgery and radiotherapy, a dependence on lower levels of evidence before clinical adoption persists, the reasons for which are multifaceted.[20,29–37] Hence, a rapid uptake of new surgical and radiotherapy technologies has been observed, even without robust comparative effectiveness data that supports one modality over another.[38] This uptake might be further stimulated by the fact that new treatments (eg, technologies and medicines) are often presented as breakthroughs or game changers in the absence of clear evidence.

	ESMO-MCBS	ASCO-VF	NCCN-B
Cancer types			
Solid tumours	Included	Included	Included
Haematological malignancies	Not included	Included	Included
Treatment intent			
Curative/adjuvant	Included	Included	Not stated
Palliative	Included	Included	Not stated
Treatment modalities			
Systemic anticancer therapies	Included	Included	Included
Radiotherapy	Not included	Not included	Not stated
Surgery	Not included	Not included	Not stated
Development team			
Physicians	Included	Included	Included
Nurses	Not included	Not included	Not included
Epidemiologists	Not included	Not included	Not included
Statisticians	Included	Not stated	Not included
Patients	Not included	Not included	Not included
Patient advocates	Not included	Not included	Not included
Public	Not included	Not included	Not included
Intended users and stakeholders			
Patients	Not included	Included	Included
Providers	Not included	Included	Included
Payers	Included	Not included	Not included
Policy makers	Included	Not included	Not included
Public	Not included	Included	Not included

ESMO-MCBS=European Society for Medical Oncology Magnitude of Clinical Benefit Scale. ASCO-VF=American Society of Clinical Oncology Value Framework. NCCN-B=National Comprehensive Cancer Network Blocks.

Table 1: **General aspects of value frameworks**

For the **UK National Institute of Health and Care Excellence** see https://www.nice.org.uk/

For the **American Institute for Clinical and Economic Review** see https://icer-review.org/

A position paper by the European CanCer Organisation (ECCO)[39] showed the need for a public policy debate on access to innovation beyond the current policy focus on new pharmaceutical treatments. It questioned how to expand access to improved diagnostic procedures and more effective forms of surgery and radiotherapy whilst ensuring multidisciplinary health-care remains sustainable for all patients with cancer across Europe. The paper also calls for more consistent measurement of the value of any innovation that is rooted in a common understanding of its clinical effectiveness and added value to patients.[39]

The current project was performed by a multi-stakeholder taskforce of medical, policy, and patient advocacy experts representing ECCO, the European Society for Radiotherapy and Oncology (ESTRO), the European Society of Surgical Oncology, and the European Organisation for Research and Treatment of Cancer. Although formal endorsement by each separate organisation was not carried out, the project took place under the oversight of the ECCO Oncopolicy Committee, which was acting on behalf of ECCO's 28 member organisations regarding policy projects and documents. In this Review, three existing cancer value frameworks are evaluated and RCTs in radiation and surgical oncology are tested with two of these tools. Subsequently, the challenges in defining a robust and transparent mechanism that can better, and more consistently, appraise the value of new loco-regional cancer treatments, are addressed.

Value frameworks in oncology: the current status

The increasing narrative around value-based health care has led to several initiatives seeking to assist the development of a more consistent definition of the clinically meaningful benefit and value of treatments. Our analysis focused on three value frameworks specifically developed for the context of oncology: the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS), the ASCO Value Framework (ASCO-VF), and the NCCN Blocks (NCCN-B).[9–13] These are the main tools that have been used in the medical research literature for considering the value of oncology interventions, specifically for drug treatments.[40,41] Additionally, information on the development of these scales has been published to enable detailed appraisal of their methods, unlike information on the development of other scales, such as the Memorial Sloan Kettering Cancer Center's Drug Abacus, of which the methodological description is not available in publications. Moreover, these three value scales that this Review focuses on differ methodologically from the approach used by HTA bodies such as the UK National Institute of Health and Care Excellence framework and the American Institute for Clinical and Economic Review framework. Value scales appraise both the strength of clinical evidence and the expected added benefit for the patient of a particular intervention, whereas HTA tools tend to focus on whether an intervention meets a predefined threshold for cost per outcome.

The general aspects of the three value scales are shown in table 1.[9–13] ESMO-MCBS and ASCO-VF were specifically developed to appraise the value of oncology medicines in the curative and palliative setting, whereas NCCN-B does not specify treatment modalities nor intents. ASCO-VF and NCCN-B cover haematological malignancies and solid tumours, whereas ESMO-MCBS only focuses on solid tumours. Clinicians have been the primary drivers in the development of these three value tools. Patients and the public, on the other hand, were not consulted in the initial development of these tools, although both were the intended end users for ASCO-VF, whilst only patients were the intended end users for NCCN-B. ASCO-VF and NCCN-B also aim to provide professional peer support for clinicians, which is in contrast with ESMO-MCBS, in which the primary aim is to inform payers and policy makers of the value of new anticancer drugs to support market access. However, the nature of these frameworks is evolving through their application, and the need for patient input is increasingly being recognised.[42] For example, ESMO-MCBS has

started consultations with patients and plans the inclusion of patient input in the next iteration of its tool.[10] Similarly, reflecting the feedback from patients who emphasised that even mild side-effects can have a major effect on quality of life, the new version of ASCO-VF now considers all side-effects in its value framework, instead of only the most severe.[12]

Table 2 shows the endpoints of the different value tools. ASCO-VF and NCCN-B take into account key criteria that define value-based health care: outcomes and costs.[11–13] Conversely, ESMO-MCBS only focuses on outcome, because it recognises this as the first step to determine value in cancer care.[9,10]

Costs are addressed differently by ASCO-VF and NCCN-B. In the ASCO-VF tool, the direct costs of the treatment are defined by the drug acquisition cost (anticancer and supportive care drugs) and the related patient co-payments.[11] ASCO-VF acknowledges that other costs, such as hospital, physician visits, or costs related to work missed by the patient or caregivers, could be substantial, but they are not included in the analysis because they are not readily available nor easily quantifiable.[12] In the NCCN-B tool, the financial issue is approached more broadly as affordability, and is rated using the experts' knowledge of the overall cost of the regimen, including drug cost, supportive care, infusions, toxicity monitoring and management. This estimation of affordability by the NCCN-B, defined on a scale ranging from very inexpensive to very expensive, implies a health system perspective: it uses the costs for the health-care system and questions the interventions' affordability for the society who pays for it.[13]

A similar broader approach is taken by the NCCN-B scale regarding outcome: although it is mainly based on evidence derived from clinical trials, the knowledge is complemented by real-life evidence obtained through expert opinion, and therefore includes effectiveness data.[13] Conversely, the ASCO-VF and the ESMO-MCBS scales only focus on efficacy obtained from clinical trials.[9–12] In general, NCCN-B defines the endpoints considered in its tools less explicitly but defines outcome in terms of long-term survival, curative potential, or disease control.[13]

Overall, progression-free and disease-free survival are covered by all three value tools, either explicitly (ESMO-MCBS and ASCO-VF) or implicitly (NCCN-B). Treatment-free interval is addressed by ASCO-VF and NCCN-B, with NCCN-B also evaluating local disease control. Although toxicity is included in all three tools, palliation of symptoms is only covered in ASCO-VF and NCCN-B, whereas ESMO-MCBS was the only tool that initially incorporated quality of life in its algorithms. However, the revised version of ASCO-VF introduced quality of life in the evaluation of treatments for advanced disease, providing bonus points to the intervention evaluated through the ASCO-VF scale. It is also worth acknowledging that toxicity is typically scored at early onset during or shortly after treatment. But the revised version of ASCO-VF subtracts points in case symptomatic treatment-related toxicities do not resolve within 1 year post treatment. Similarly, in NCCN-B, a block is deduced for safety when substantial chronic or long-term toxic effects occur.[9–13]

As mentioned, NCCN-B derives its evaluation on the entire spectrum of available evidence, from meta-analyses to expert opinion.[13] ESMO-MCBS and ASCO-VF mainly define the ranking of clinical benefit on the basis of evidence from RCTs,[9,11] although ESMO-MCBS has more recently broadened this defenition to include single-arm phase 2 trials.[10] Table 3 provides an overview of the evidence included in the various tools.

Both ESMO-MCBS and ASCO-VF used a statistical approach to weigh the defined endpoints and integrate

	ESMO-MCBS	ASCO-VF	NCCN-B
Key criteria VBHC			
Outcome	Efficacy	Efficacy	Efficacy and effectiveness
Cost	Not stated	Direct cost	Affordability
Clinical endpoints			
Overall survival	Included	Included	Not stated
Progression-free survival	Included	Included	Not stated
Disease-free survival	Included	Included	Not stated
Treatment-free interval	Not included	Included	Not stated
Cause-specific survival	Not included	Not included	Not included
Response rate	Included	Included	Not included
Treatment-related mortality	Not included	Included	Not included
Locoregional control	Not included	Not included	Not stated
Organ preservation	Not included	Not included	Not included
Reintervention rate	Not included	Not included	Not included
Quality of life	Included	Included	Not included
Toxicity and safety	Included	Included	Included
Palliation of symptoms	Not included	Included	Included

ESMO-MCBS=European Society for Medical Oncology Magnitude of Clinical Benefit Scale. ASCO-VF=American Society of Clinical Oncology Value Framework. NCCN-B=National Comprehensive Cancer Network Blocks. VBHC=value-based health care.

Table 2: **Endpoints used in value frameworks**

	ESMO-MCBS	ASCO-VF	NCCN-B
Meta-analyses	Not included	Not included	Included
Phase 3 trials	Included	Included	Included
Phase 2 trials	Included	Not included	Included
Cohort studies	Not included	Not included	Not stated
Case-control studies	Not included	Not included	Not stated
Case series	Not included	Not included	Not stated
Expert opinion	Not included	Not included	Included

ESMO-MCBS=European Society for Medical Oncology Magnitude of Clinical Benefit Scale. ASCO-VF=American Society of Clinical Oncology Value Framework. NCCN-B=National Comprehensive Cancer Network Blocks.

Table 3: **Level of evidence addressed in value frameworks**

	Setting	Comparators	Objective	Trial design	Primary endpoint	Secondary endpoints
PARSPORT, Nutting and colleagues[34]	Head and neck cancer, pharyngeal SSC, primary radiotherapy	Conventional radiotherapy *vs* intensity-modulated radiotherapy	Assess whether parotid- sparing intensity-modulated radiotherapy reduces the incidence of severe xerostomia	Phase 3	Percentage of patients with grade ≥2 xerostomia 1 year after radiotherapy	Survival: OS and LR-PFS; toxicity: acute toxicity and other late side-effects; QoL and PROM: xerostomia in xerostomia-modified questionnaire; other: percentage of patients with any measurable salivary flow after radiotherapy
AMAROS, Donker and colleagues[33]	Breast cancer, positive sentinel node, adjuvant regional treatment	Axillary lymph node dissection *vs* axillary radiotherapy	Assess whether axillary radiotherapy provides comparable regional control with fewer side-effects	Phase 3, non-inferiority	5-year axillary recurrence	Survival: OS, DFS, and axillary RFS; toxicity: late toxicity (shoulder mobility and lymphoedema); QoL/PROM: symptom scores EORTC-QLQ-C30 and QLQ-BR23
APBI GEC-ESTRO, Strnad and colleagues[31]	Breast cancer, low risk after breast-conserving surgery, primary radiotherapy	Brachytherapy APBI *vs* WBI	Assess whether APBI using multicatheter brachytherapy is non-inferior to WBI with respect to local control	Phase 3, non-inferiority	Ipsilateral local recurrence	Survival and clinical: OS, DFS, and cumulative incidence of regional and distant recurrence; toxicity: acute and late toxicity; QoL and PROM: QoL non-otherwise specified; other: cosmesis and rate of contralateral breast cancer
LRT metastatic breast cancer, Badwe and colleagues[36]	Metastatic breast cancer, surgical treatment of primary disease	Surgery *vs* no surgery to primary tumour	Assess whether LR surgery improves outcome in metastatic breast cancer	Phase 3	OS	Survival: LR-RFS, distant PFS; QoL/PROM: QoL EORTC QLQ C-30 and BR23
CHIPP, Dearnaley and colleagues[30]	Localised prostate cancer, primary radiotherapy	74 Gy/37 fractions *vs* 60 Gy/20 fractions or 57 Gy/19 fractions	Efficacy and side-effects of conventional and hypofractionated radiotherapy	Phase 3, non-inferiority	Time to biochemical or clinical failure	Survival and clinical: OS, DFS, development of metastases; toxicity: acute bowel and bladder toxicity: peak and at 18 weeks, late grade ≥2 toxicity at 2 years and 5 years, time to development of grade 1–3 toxicity; QoL/PROM: symptom scores in UCLA-PCI and EPIC-50; other: recommencement of hormonal treatment for disease recurrence
ROLARR, Jayne and colleagues[32]	Rectal cancer, primary laparoscopic surgery	Robotic-assisted *vs* conventional laparoscopic surgery	Assess risk of conversion to open laparotomy	Randomised, unblinded, parallel-group trial	Rate of conversion to open surgery	Survival and clinical: 30 days mortality and local recurrence; complications: intraoperative complications; QoL: 36-Item Short Form Survey and 20-item Multidimensional Fatigue Inventory; PROMs: bladder and sexual function in International Prostate Symptom Score, International Index of Symptom Score, International Index of Erectile Function, and Female Sexual Function Index; and other: margin status, quality of the plane of surgery
STAMPEDE, Parker and colleagues[35]	Metastatic prostate cancer, radiotherapy of primary tumour	Standard of care for metastatic prostate cancer, with or without radiotherapy	Assess survival benefit of adding radiotherapy to primary tumour	Phase 3	OS (failure-free survival for the interim analysis)	Survival: PFS, M-PFS, and prostate cancer-specific survival; toxicity: symptomatic local events

APBI=accelerated partial breast irradiation. DFS=disease-free survival. EORTC=European Organisation for Research and Treatment of Cancer. LR-PFS=local-relapse progression-free survival. LR=local relapse. LRT=locoregional therapy. M-PFS=metastatic progression-free survival. OS=overall survival. PFS=progression-free survival. PROM=patient-reported outcome measurement. RFS=relapse-free survival. SCC=squamous cell carcinoma. QoL=quality of life. WBI=whole-breast irradiation.

Table 4: **Analysis of trial design and endpoints used in seven randomised controlled trials in radiation or surgical oncology**

them into a formal value metric, ranking the magnitude of clinically meaningful benefit and the net health benefit. As such, these tools enable comparative analysis of the value of different anticancer drugs.[9–12] NCCN-B shows the results of its appraisal visually by using Value Blocks.[13]

Defining relevant endpoints from a multi-stakeholder perspective

The available value tools in oncology mainly target systemic anticancer treatments rather than locoregional cancer interventions, such as radiotherapy and surgery. Additionally, as shown in table 2, the existing frameworks are essentially built around four outcomes to measure benefit to the patients, reflecting market authorisation requirements: overall survival, progression-free survival, safety, and health-related quality of life. However, when it comes to gauging the benefit of locoregional therapies it is likely that the frameworks should be more nuanced than those used to assess drugs, reflecting the specificities of locoregional treatments. Beyond the mere issue of survival or prolongation of life, endpoints such as symptom control, organ preservation, peri-operative and post-operative complications, or functional outcomes are also of great importance. Such endpoints are absent from the current value framework tools evaluating clinically meaningful benefit.

Additionally, not all of these endpoints will be relevant to every surgical or radiotherapeutic innovation, but

	Improvement of OS	Improvement of DFS	Reduced treatment toxicity or improved QoL	Reduced treatment cost	Magnitude of Clinical Benefit Grade
PARSPORT, Nutting and colleagues[34]	2-year OS was 76% conventional radiotherapy *vs* 78% IMRT; 2-year OS HR was 0·68 (95% CI 0·34–1·37)	Not reported	Proportion of patients with grade ≥2 xerostomia at 1 year was 74% with conventional radiotherapy *vs* 38% with IMRT (p=0·0027); grade ≥2 acute fatigue was 41% with conventional radiotherapy *vs* 74% with IMRT, p=0·0015; significant benefits in recovery of saliva secretion with IMRT; clinically significant improvements in dry mouth-specific and global QoL with IMRT	Not reported	Form 1: grade B; reduced toxicity (xerostomia) and improved QoL
AMAROS, Donker and colleagues[33]	5-year OS was 93·3% LND *vs* 92·5% radiotherapy; 5-year OS HR was 1·17 (95% CI 0·85–1·62)	5-year DFS was 86·9% LND *vs* 82·7% radiotherapy; 5-year DFS HR was 1·18 (95% CI 0·93–1·51)	Clinical lymphoedema at 5 years was 23% *vs* 11% (p<0·0001); 10% arm circumference increase at 5 years was 13% *vs* 5% (p=0·0009); shoulder mobility at 5 years was no difference; no significant differences in QoL	Not reported	Form 1: grade B reduced toxicity
APBI GEC-ESTRO, Strnad and colleagues[31]	5-year OS was 95·55% WBI *vs* 97·27% APBI (p=0·11) and HR was not reported	5-year DFS was 94·45% WBI *vs* 95·03% APBI (p=0·79); HR was not reported	5-year grade 2–3 late skin side-effects was 5·66% with WBI *vs* 3·23% with APBI (p=0·0807); 5-year grade 3 fibrosis was 0·23% with WBI *vs* 0% with APBI (p=0·4561); 5-year grade 3 breast pain was 3·17% with WBI *vs* 1·14% with APBI (p=0·0389)	Not reported	Form 1: grade B reduced breast pain
LRT metastatic breast cancer, Badwe and colleagues[36]	2-year OS was 41·9% LRT *vs* 43·0% no LRT; 2-year OS HR was 1·04 (95% CI 0·81–1·34)	Not reported	Apart from one grade 3 adverse event (wound infection) in the LRT group, no other adverse events were reported; QoL was not reported	Not reported	Form 2a: grade 1 no OS benefit observed (ie, no benefit from surgical intervention)
CHIPP,* Dearnaley and colleagues[30]	5-year OS HR was 0·78 (95% CI 0·57–1·05)	5-year DFS HR was 0·83 (95% CI 0·68–1·01)	Worse acute bowel toxicity was 25% with 74 Gy *vs* 38% with 60 Gy; no difference in acute bladder toxicity; no difference in late toxicity at 5 years; and no difference in PROMs at 5 years	Not reported	Form 1 was not gradable; but grade B if expected lower cost of hypo-fractionation would be factored in
ROLARR, Jayne and colleague[32]	Not reported	Not reported	No difference in intra-operative complications; no difference in 30-day complications; no difference in complications at 6 months; no difference in bladder or sexual function at 6 months	Higher cost of robotic-assisted laparoscopic surgery	Form 1 was not gradable because the study did not show superiority of the investigational approach
STAMPEDE, Parker and colleagues[35]	All cases*: 3-year OS was 62% with no radiotherapy *vs* 65% with radiotherapy; HR 0·92 (95% CI 0·80–1·06); cases with low metastatic burden*: 3-year OS was 73% with no radiotherapy *vs* 81% with radiotherapy; HR:0·68 (95% CI 0·52–0·90)	Not reported	Some radiotherapy toxicity, but no difference in symptomatic local event-free survival	Not reported	Form 2a was not gradable; total population* had no OS gain; cases with low metastatic burden*: HR was <0·70 but median OS not reached

All trials are evaluated with the European Society for Medical Oncology Magnitude of Clinical Benefit Scale v1.1 form 1, except for the trial of Badwe and colleagues,[36] for which form 2a for OS with the standard treatment >12 and <24 months was used, and of Parker and colleagues, for which form 2a for median OS with the standard treatment >24 months was used. Improvement in pathological complete response was not included in the table. APBI=accelerated partial breast irradiation. Conv=conventional radiotherapy. DFS=disease-free survival. HR=hazard ratio. IMRT=intensity-modulated radiotherapy. LND=lymph node dissection. LRT=locoregional therapy. OS=overall survival. QoL=quality of life. WBI=whole-breast irradiation. *Comparison only for 74 Gy versus 60 Gy.

Table 5: **Analysis of trials according to ESMO-MCBS**

instead depend on the cancer type, the treatment intent, and the nature of the intervention evaluated, whether it is new technologies, treatment techniques, or treatment schedules, which could be in combination or not with systemic drugs.[43] Table 4 describes the endpoints used in seven RCTs that explore the role of surgery and radiotherapy in prostate, colorectal, head and neck, and breast cancers.[30–36] Although traditional endpoints are relevant in these studies, the primary focus is often centred around improving local control and long-term function,[30,31,33] or reducing operative complications and acute and late toxicity,[32,34] which are neglected—or not given sufficient weightings—in the scoring system of current value frameworks.

For example, local control that allows organ sparing and function preservation could have a substantially positive effect on the wellbeing of the patient. Examples include those where the glottis, the breast, or a limb can be spared or cosmesis or function improved because of a judicious choice between radiotherapy and surgery, or a combination of radiotherapy with less mutilating surgery. The AMAROS trial is one example of a trial that uses a combination of radiotherapy with less mutilation surgery in the setting of breast cancer.[33] Local control, or at least reduction of local tumour burden, is also crucial in relieving symptoms.[44]

For toxicity, it is important to emphasise the distinction between acute toxic effects that could be unavoidable and

	CB; OS; DFS (PFS)*; response rate	Toxicity; grading of acute toxicity and unresolved treatment-related toxic effects after 1 year	Bonus points; tail of the curve, palliation, QoL, and treatment-free interval*	Net health benefit
PARSPORT, Nutting and colleagues[34]	2-year OS HR was 0·68 (95% CI 0·34–1·37); median OS was not reported; DFS HR was not reported; and unresolved symptomatic treatment-related toxic effects lower after IMRT	Acute side-effects 0·5 point higher in IMRT	OS curves not reported	Adjuvant form not gradable; no difference in survival acute toxicity similar and decrease in late toxicity cannot be rewarded
AMAROS, Donker and colleagues[33]	5-year OS HR was 1·17 (95% CI 0·85–1·62); 5-year DFS HR was 1·18 (95% CI 0·93–1·51); unresolved symptomatic treatment-related toxic effects lower after RT	Acute toxicity not reported	Tail of the curve bonus not applicable	Adjuvant form not gradable; no difference in survival and decrease in late toxicity cannot be rewarded
APBI/GEC-ESTRO, Strnad and colleagues[31]	HR OS was not reported; no difference in OS; median OS not reported; HR DFS not reported, no difference in DFS unresolved symptomatic treatment-related toxic effect slower after APBI	Acute toxicity not reported; no difference	Tail of the curve bonus not applicable	Adjuvant form not gradable; no difference in survival and decrease in late toxicity cannot be rewarded
LRT metastatic, breast cancer Badwe and colleagues[36]	2-year OS HR was 1·04 (95% CI 0·81–1·34); no difference in unresolved symptomatic treatment-related toxic effects	Acute toxicity not reported	Palliation bonus not applicable; QoL bonus not applicable; and treatment-free interval bonus not applicable	Advanced form not gradable; no difference in survival; and no difference in other outcomes
CHIPP †,Dearnaley and colleagues[30]	5-year OS HR was 0·78 (95% CI 0·57–1·05); 5-year DFS HR was 0·83 (95% CI 0·68–1·01); and no difference in unresolved symptomatic treatment-related toxic effects at year 5	Acute toxicity reported for grade ≥2; and no separate evaluation possible for grades 1–2 and grades 3–4	Tail of the curve bonus not applicable	Adjuvant form not gradable; no difference in survival; and no difference in other outcomes advantage shorter fractionation schedule cannot be rewarded
ROLARR, Jayne and colleagues[32]	OS HR not reported; median not reported; and DFS HR not reported	Acute toxicity not reported; no difference in complications at 30 days and 6 months	Tail of the curve bonus not applicable	Adjuvant form not gradable; and no difference in survival, no difference in other outcomes
STAMPEDE, Parker and colleagues[35]	For total population*: 5-year OS HR was 0·92 (95% CI 0·80–1·06); slightly higher grade 3–4 late toxicity after radiotherapy 4% *vs* no radiotherapy 1%; for low metastatic subgroup*: 5-year OS HR was 0·68 (95% CI 0·52–0·90)	Acute radiotherapy-related toxicity reported lower for weekly than for daily schedule; symptomatic local events similar	Palliation bonus not applicable; QoL bonus not applicable; treatment-free interval bonus not applicable, time to any therapy similar; tail of the curve bonus applicable; no palliation, QoL, or TFI applicable; and bonus was 20 points	The advanced form was not gradable for the total population; for the low metastatic subgroup, scoring with the advanced form resulted in a CB of 32 and 0 toxicity, which allowed adding 20 bonus points, resulting in a net health benefit of 52

All trials are evaluated with the American Society of Clinical Oncology Value Framework (ASCO-VF) updated form for adjuvant therapy, except for the trials of Badwe and colleagues[36] and Parker and colleagues,[35] for which the advanced disease form was used. Improvement in pathological complete response was not included in the table. Only net health benefit was evaluated; no evaluation of treatment costs was included as ASCO-VF focuses on drug acquisition costs only. CB=clinical benefit. OS=overall survival. DFS=disease-free survival. PFS=progression-free survival. TFI=treatment-free interval. HR=hazard ratio. QoL=quality of life. APBI=accelerated partial breast irradiation. IMRT=intensity-modulated radiotherapy. LRT=locoregional therapy. RT=radiotherapy.*Applies to evaluation in the advanced form. †Comparison only for 74 Gy versus 60 Gy.

Table 6: **Analysis of trials according to ASCO-VF**

acceptable in case of treatments with curative intent and late toxic effects, occurring months to years after treatment especially for radiotherapy, which should be minimised as much as possible. Innovations in radiotherapy often focus on decreased long-term toxicity and the consequential effect on quality of life.[20,31,33,34] Additionally, better techniques could allow the reduction of the intensity, duration, and financial cost of toxicity of a treatment compared with existing standards without compromising functional or oncological outcomes.[30]

Tables 5 and 6 also show the evaluation of the selected trials using the ESMO-MCBS tool (version 1.1: form 1 for curative intent and form 2a for the metastatic setting, which accounts for survival with standard treatment) and ASCO-VF (both for the adjuvant setting and advanced disease).[10,12] Appraisal with NCCN-B was not performed because NCCN-B is essentially a tool for evidence synthesis for a particular intervention with no real assessment of comparators within trials.[13] Although all evaluated trials have informed and affected practice[29]—or are expected to do so—they either resulted in low clinical benefit grades because of their sole effect on toxicity and quality of life,[31,33,34] or turned out difficult to appraise with the current value frameworks as the trial endpoints used were not reflected in the tools. This situation shows that the selection of endpoints is crucial when considering the value of new locoregional cancer treatments, as well as differentiating between surrogates and hard endpoints that have influenced the weightings applied in the scales discussed.

Several questions remain following this evaluation. Do we have the adequate tools to define the relative benefits and value of different treatment approaches for the same indication? Are the available tools ready to capture additional aspects of care that matter to patients, such as shorter and less intensive treatment schedules and the

ability to return to normality or to return to work? Patient advocates show that framing value is complex and ultimately not compatible with one single homogeneous set of patient values.[42,45] It is influenced by external factors such as the health-care, social, religious, and cultural environments, and patient-specific factors such as age, gender, education, and personal finances. To capture this rich spectrum of values, frameworks should consider not only the clinical effects of a treatment but also its practical burden that impacts patients' wellbeing, and they should attempt to incorporate the broader range of outcomes that patients could regard as most relevant.[42]

The ICHOM has gone beyond traditional endpoints of survival and disease control. It does not appraise the quality of evidence or degree of benefit, but instead recommends a range of outcome measures and instruments that they consider best captures value from the patient perspective. Standard sets of patient-centred outcome measurements have been developed for various medical conditions,[14] including breast, lung, colorectal and prostate cancers.[46–50] Table 7 shows the main differences and overarching aims and methods between the ICHOM and the other three scales described. The ICHOM includes outcomes that pertain to the entire disease history of a patient, such as long-term treatment complications, the degree of health that can be recovered, and the quality of death. ICHOM aims to standardise patient outcomes routinely collected in clinical practice and trials to reflect the diverse range of benefits that new and existing interventions could offer to patients, and to allow benchmarking as part of quality assurance processes following clinical adoption. The importance of a multi-stakeholder approach to identify endpoints for new interventions in the context of trials and for processes of care has stimulated several tumour-specific initiatives that develop core outcome sets in cancer surgery (eg, in oesophageal and colorectal surgery).[51,52]

ESMO-MCBS, ASCO-VF, NCCN-B	ICHOM
Evaluation	Recommendation
Ranking	Benchmarking, quality improvement
Measuring magnitude of benefit	Definition of outcome measures
Focusing on treatments	Addressing the entire disease history
Composite value scale	Indicators of quality
No current patient involvement	Patient-centric, shared decision making
By clinicians representing organisations	By independent clinicians and patients
Level of evidence essential	Various evidence allowed
Retrospective	Prospective
Oncology	Diseases beyond oncology

ESMO-MCBS=European Society for Medical Oncology Magnitude of Clinical Benefit Scale. ASCO-VF=American Society of Clinical Oncology Value Framework. NCCN-B=National Comprehensive Cancer Network Blocks. ICHOM=International Consortium for Health Outcomes Measurement.

Table 7: **Comparison between value frameworks and ICHOM**

How to appraise the outcome of locoregional cancer treatments: a question of evidence

The development of a value framework for locoregional cancer treatments poses various challenges, in particular how to overcome the issue of the different levels of evidence available regarding patient benefit when compared with systemic therapies. Available value frameworks are mainly based on evidence from RCTs (table 3), which are less common when assessing new technologies in surgical or radiation oncology. An evaluation of global radiotherapy research between 2001 and 2015 showed that only 5% of publications were devoted to clinical trials.[43] In their absence, small-scale observational studies and more latterly modelling studies have been used as the evidence standard for many new technologies before clinical adoption. In circumstances where the minimum requirement by regulators is to show safety, the use of lower evidence levels could bear the risk of integrating low-value technologies that are both expensive and unlikely to deliver tangible improvements in the experience and outcome of patients.

One observed barrier is that funding for trials of non-pharmaceutical technologies lags behind that for trials of pharmaceuticals; for example, only 5% of cancer funding goes into surgical trials.[37] However, assessing innovation in surgery and radiotherapy is also inherently more complex than assessing new cancer drugs, and RCTs that include a surgical or radiotherapeutic technique might not be feasible or appropriate in every indication.[53,54]

In radiotherapy, innovations can include everything from the assessment of a new treatment indication and new treatment schemes (eg, different doses and fractionation schedules and novel combinations with systemic drugs), to new techniques for targeting and localising the tumour (eg, imaging before and during radiotherapy) or treatment delivery (eg, intensity-modulated radiotherapy, stereotactic body radiotherapy). They also include irrradiation with different biological entities (eg, protons) as well as new technologies (eg, magnetic resonance-based radiotherapy) and methods of immobilisation (eg, masks). In addition to the range of relevant endpoints for surgery and radiotherapy trials (table 4) the level of evidence required to show improved outcome might also vary.[54] It could be argued that a new fractionation schedule or a new combination treatment requires assessment in an RCT, whereas the integration of a new immobilisation mask might allow a lower level of evidence. Other innovations, such as those requiring investment in a new technology, might need a more blended or model-based approach to evidence generation.[20,53] Furthermore, high upfront capital investments associated with new technologies, typically made by health-care providers before their clinical validation, and the risk that innovations could quickly

become outdated because of rapid and incremental developments in software and hardware explain why RCTs can be difficult to accomplish for radiotherapy technologies.[20,55]

Similarly, surgical innovations could entail the development of more advanced surgical techniques that allow more complete tumour resections (eg, total mesenteric excision) or decrease morbidity while obtaining the same level of local control (eg, sleve lobectomies obviating the need for pneumonectomy). Crucially, this evolution could be related to the introduction of new technologies, of which some could become popular well before being formally tested in a trial. An archetypal example is laparoscopic surgery, which was introduced in the mid-1980s and widely disseminated before any quality control occurred, yet its introduction resulted in shorter hospital stay, improved quality of life and better access to surgical treatment in some clinical settings. Unfortunately, such evidence of superior outcomes are not de facto seen for all new surgical technologies (eg, robotic surgery) and not across all indications.[56] In other situations the technique on its own might not be objectively better, but could be taught and disseminated more optimally by instructing young surgeons on a lab or virtual model, and therefore provide improved outcomes as a consequence of better training. The use of RCTs in surgical oncology might be compromised because of issues related to investment in equipment, training of the dedicated personnel, and to surgical techniques evolving progressively while skills are being enhanced and new tools brought to use. Furthermore, it has been observed that one out of five surgical oncology trials are abandoned because it is usually highly complex to set-up multicentre trials in surgery and little funding and operational support are available to run the trials.[57]

Finally, the value of locoregional interventions and outcomes obtained crucially depend not only on the operators (physician and nurses) but also on the quality of the equipment and on a broad range of other professionals involved (eg, physicists and dosimetrists in the case of radiotherapy and anaesthesia and post-operative care in surgery).[36] Therefore, any benchmarking of the expected value or benefit (measured in terms of patient outcome) of a new surgical or radiotherapeutic intervention must take into account the quality of its delivery.[57–59]

Although these aspects challenge the design and execution of trials for locoregional oncology treatments, it remains important that high-cost innovations undergo robust evaluation as the evidence deficit can adversely affect reimbursement decisions, delay clinical adoption of innovations, and potentially facilitate widespread adoption of interventions that offer no benefit or can result in harm.[60] Guidance regarding the research methods and studies needed to provide adequate evidence on benefit or added benefit is a prerequisite for a framework that assesses the clinically meaningful benefit of new locoregional interventions.[61] The IDEAL (idea development, exploration, assessment, and long-term follow-up) framework was developed to provide a basis for such guidance in the field of surgery.[54] It emphasises the need to ensure the validity and quality of studies during the earlier stages of technical development and before RCTs. This step would facilitate refinement of the procedure, community education, and consideration of alternative indications as part of the early development phase. Moving away from single-centre, retrospective series as a basis for evidence generation and before considering an RCT, the authors of the IDEAL recommendations suggest a stepwise collaborative collection of non-randomised prospective data that focuses on feasibility outcomes, adverse event analysis, patient-reported outcome measures, and clinical outcomes. RCTs are expected to account for surgical learning curves, blinding or masking of outcome assessors, assessment of the quality of surgery undertaken, and reporting of main outcomes according to guidelines such as CONSORT. The IDEAL framework is being used by research funders to support prospective multicentre exploration studies to inform future RCTs and by HTA communities for the assessment of medical technologies and devices.[62,63] Based on this surgical experience, IDEAL has been adapted to radiation oncology (R-IDEAL) to provide guidance for evidence generation for radiotherapy innovations. It is implemented for the clinical evaluation of MRI-guided radiotherapy.[64] Fundamental in this proposal is the fact that radiotherapy effects can be modelled, allowing the prediction of potential treatment benefits, and hence facilitate patient selection for specific techniques or technologies. Early predicate and modelling studies are therefore included in the proposal, whereas the ambition to include randomisation at an early stage of technology development and the need for long-term follow-up for late effects were underlined.

Such frameworks could support the definition of different scoring weights in a clinical benefit scale, depending on the appropriateness of the evidence underpinning the observed benefit.

Value: the balance between outcome and costs

In the context of increasing health-care expenses and budgetary restrictions, health economic evidence has become a prerequisite before granting reimbursement for new health-care interventions. Economic evaluations analyse the additional costs incurred and the incremental outcomes gained by delivering a new intervention compared with existing alternatives of care. The resulting ratio, the incremental cost-effectiveness ratio provides the balance between costs and outcomes—during treatment and in the years thereafter—and is used to inform stakeholders that plan, provide, or pay for the health services under evaluation.[65]

In oncology, this type of analysis, part of a broader HTA programme, is almost standard for new anticancer

drugs. Yet, such rigour is not typically applied to the adoption of technologies. Reasons underlying this lack of transference are a combination of scarce availability of comparative effectiveness data and the incremental nature of technology evolution, resulting in difficulties in accurately capturing real costs and long-term clinical outcome.[20,55] Additionally, health economic evaluations are often erroneously perceived as a means to cut costs or to block or slow down access to innovative treatment strategies that are often more expensive. At a European level, discussions are ongoing to harmonise HTA programmes of drugs and technologies; however, no consensus has been reached as yet.[27,28]

In essence, Porter's definition of value also addresses this balance between costs and outcomes, yet the central focus is shifted towards increasing value through improved outcome for patients (ie, optimising health outcomes achieved per dollar spent).[8] Although the available value frameworks all provide a method to define clinical benefit, their approach regarding the costs differs (table 2). ESMO-MCBS does not consider costs,[9,10] ASCO-VF includes the costs of the medicine to the health-care system and the patient without consideration of other costs,[11,12] and NCCN-B includes economic considerations by defining affordability in a broad sense.[13]

In the examples of ASCO-VF and NCCN-B, the costs are determined by their reimbursement tariffs.[11–13] Although they could represent the cost from a health-care perspective, they have typically been defined through negotiations and hence are not necessarily a good proxy for the real costs of the intervention.[66] According to Kaplan and Porter[67] one of the major problems of current health-care systems is the scarcity of good cost data obtained with validated cost-accounting methods. Accurate resource cost data are indeed scarce in radiotherapy and the use of validated cost-accounting models is infrequent.[22,66] The same scarcity is observed in surgery. Yet, in view of allocating the adequate payment to each individual intervention, accounting for its degree of technical and clinical complexity, the importance of understanding the cost of new and established health-care interventions cannot be overstated.[68] To address this need in radiotherapy, ESTRO's Health Economics in Radiation Oncology project has developed a time-driven activity-based costing model to calculate the cost of external-beam radiotherapy at a national level.[69,70]

Towards an evidence-informed value framework for surgical and radiation oncology

Two main considerations emerge from this analysis with respect to developing a value framework for surgical and radiation oncology treatments. First, for each specific intervention it is important to capture the relevant endpoints that matter most to patients, in the context of a particular oncological setting and indication. Second, one must consider how evidence is generated given the heterogeneity across radiotherapy and surgical treatment strategies. Both aspects should form the cornerstone of a clinically meaningful benefit scale—or scales—that appraise new interventions in locoregional cancer treatment. In the development of such a framework, two core steps and a series of evaluations should be undertaken.

Step one: defining core sets of endpoints for locoregional cancer treatments by multi-stakeholder collaboration

Recent projects have shown the feasibility of involving multiple stakeholders to develop a set of core outcome measures primarily reflecting the needs of patients undergoing surgery for specific cancers.[51,52] Conversely, ICHOM has defined outcome sets for specific cancer types across therapeutic interventions.[14,41–45] Building further on such experiences, the harmonisation of outcome sets for surgical and radiation oncology interventions would facilitate the development of clinically meaningful benefit scales that prioritise endpoints defined through multi-stakeholder engagement.

Although the challenge will be in finding the acceptable balance between harmonisation and specificity towards

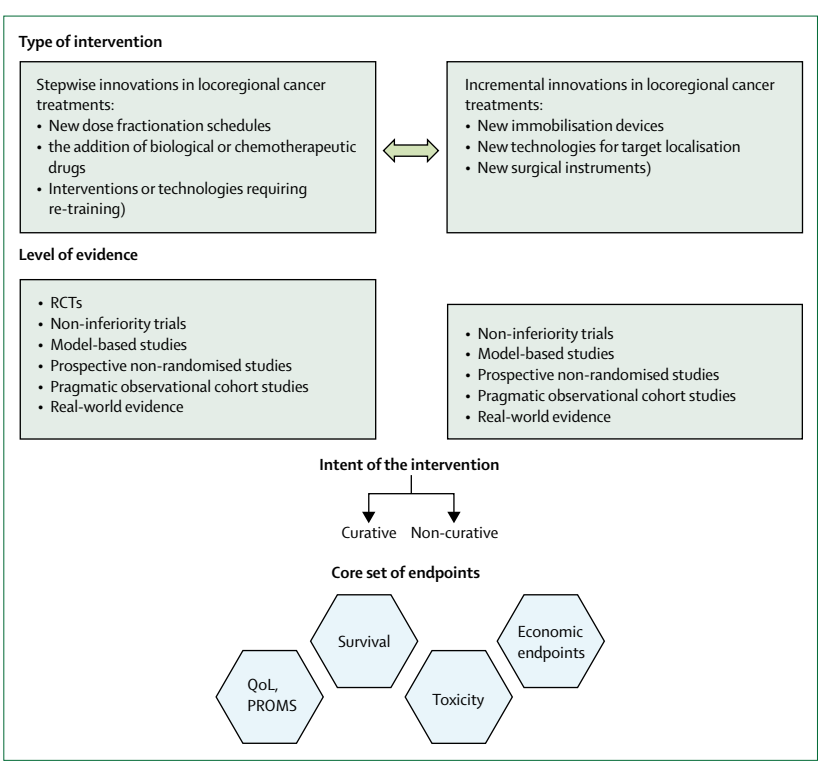

Figure: **Core aspects to consider in the development of an evidence-informed value scale for surgical and radiation oncology**

Four different aspects should be accounted for in the development of a value scale for surgical and radiation oncology: (1) distinguish between innovations that evolve stepwise and those that evolve incrementally; (2) develop a grading system including various levels of evidence and considering the respective types of innovation; (3) differentiate between curative and non-curative intent; (4) define, through multi-stakeholder collaboration, a core set of endpoints, including survival, toxicity, complications and functional outcomes, quality of life and patient-reported outcomes, and economic and operational endpoints. RCT=randomised controlled trial. QoL=quality of life. PROMS=patient-reported outcome measures.

Search strategy and selection criteria

This Review was prepared by a taskforce mandated by the Board and the Oncopolicy Committee of the European CanCer Organisation (ECCO), which comprises medical, policy, and patient advocacy experts. Besides ECCO and its Patient Advisory Committee, the authors represent the European Society for Radiotherapy and Oncology, the European Society of Surgical Oncology, and the European Organisation for Research and Treatment of Cancer. Value frameworks were evaluated and selected following expert consensus, supported by the fact that they are developed by large professional bodies, are broadly studied in the literature on value in oncology, and allow methodological appraisal. The references included were identified by the experts and no systematic literature review was performed. An extraction table was defined upfront, on the basis of which three collaborators (AA, CG, and YL) extracted the data from the articles. These were subsequently discussed and agreed upon in a live meeting where all co-authors (except KO) participated. The results were subsequently summarised in tables 1–3 as presented. The surgical and radiation oncology clinical trials that were evaluated with these frameworks were indentified by two experts (AA and YL), on the basis of their practice-changing potential (eg, if the results of the trials were integrated in practice guidelines) and reflecting a variable range of indications, cancer types, and interventions. The appraisal was performed by the same two authors.

the type of cancer and the type of intervention, such commonly agreed-upon core sets of endpoints should enable comparative evaluation of a large body of different intervention studies.

Step two: creating a clinically meaningful benefit scale for surgical and radiation oncology treatments

Creating such a scale will require substantial conceptual development and testing because of the complexities outlined in this Review. The figure shows the core aspects that in our view would need to be considered beyond those used in ESMO-MCBS and ASCO-VF. First separation of the types of interventions into two broad groups should be considered: new interventions that can be regarded as innovations potentially improving outcome in a stepwise fashion (eg, new dose fractionation schedules in radiotherapy, the addition of systemic drugs to standard radiotherapy or surgery practice, and interventions or technologies requiring retraining) versus those that represent incremental technological innovations (eg, new immobilisation devices, new techniques for target localisation, and new surgical instruments). This separation is proposed as it is likely that the evidence requirement before clinical integration for these two groups should be different, with stepwise innovations necessitating more robust prospective or randomised evaluation because of the effect on long-term survival, toxicity, and quality of life. Table 4 includes many such studies. The other type of innovations reflect the incremental upgrades that are continuously being undertaken to radiotherapy hardware and software with the aim of achieving greater efficiency, safety, and improving usability; or the continuum of evolving surgical instruments and techniques that are designed to facilitate the intervention and ameliorate outcomes. Although conceptually logical and pragmatic, such a clear distinction between stepwise and incremental innovations might not always be evident. Second, different levels of evidence beyond the formal RCT should be considered, such as non-inferiority trials, model-based studies, prospective non-randomised or pragmatic observational cohort studies, as well as real-world evidence.[61,71,72] A grading system will have to be developed that will reflect the hierarchy of this evidence in view of the type of intervention and the various endpoints considered. Third, similar to the approach in ESMO-MCBS, it remains important to consider the intent of the intervention (curative versus non-curative), especially for stepwise innovations because this consideration will influence both the endpoints defined and the magnitude of improvement that should be achieved to be meaningful. As the typical boundaries between localised (curative) and disseminated (non-curative) disease are currently fading (eg, in oligometastatic disease) this distinction is not trivial. Lastly, it is our view that endpoints in the core sets of endpoints, defined through multi-stakeholder collaboration, should be categorised into groups that consider: (1) survival including overall survival, but potentially encompassing a broader range of survival endpoints as shown in the evaluated trials; (2) toxicity, complications, and functional outcomes, where a clear distinction between the relative effect of acute and late (chronic) effects should be given attention; (3) quality of life and patient-reported outcomes using validated scales; and (4) economic and operational endpoints including resource use, costs, and quality.

Within and across these categories, endpoints will have to be weighted and scaled by considering the value they represent for the patients affected by different cancer types. In our view the inclusion of economic endpoints into the core endpoints is important in order to define more explicitly the value of new health-care interventions, especially in the context of non-inferiority studies.

Conclusion

The multi-stakeholder international oncology community needs to provide direction on the outcomes most valued by patients, the levels of evidence that are acceptable when considering the merits of new technologies in patient populations, and what evidence is required before rapid clinical adoption. The existence of an initial benchmarking of the value of new drugs by regulatory agencies who grant or do not grant market authorisation has greatly facilitated the development of value scales for systemic anticancer treatments. A similar assessment should be developed for locoregional cancer therapies,

such as surgery and radiotherapy. Such a mechanism, ideally in the form of a practical tool or scale, should include evidence from real-world (ie, data from patients treated in daily practice) and clinical trials and include the whole spectrum of patient-centred endpoints. This type of scale could help optimise patient access to high-value developments in surgery and radiotherapy, ultimately raise the evidence bar for new innovations introduced into clinical practice, and ensure that investment in research and development provides the opportunity for substantial improvement in cancer care.

Contributors

YL, AA, RP, CG, and LC researched data for this manuscript. YL, AA, RA, CG, LC, and KO drafted the original manuscript. All authors reviewed and edited the manuscript. All authors equally contributed to the discussion of the manuscript's content.

Declaration of interests

KO is chair and co-director of the International Brain Tumour Alliance, which has received grants for its work programme from Magforce, Elekta, Bristol-Myers Squibb, Novocure, AbbVie, Pfizer, Medac, Photonamic, Novartis, Celldex, Lilly, Northwest Biotherapeutics, VBL, Roche, and Apogenix. KO reports receiving personal fees from Bristol-Myers Squibb outside the context of the submitted work. YL reports receiving personal fees from AstraZeneca outside the context of the submitted work. All other authors declare no competing interests.

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