Radiotherapy and Oncology 141 (2019) 14–26

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Review Article

Critical review and quality-assessment of cost analyses in radiotherapy: How reliable are the data?

Noémie Defourny [a,*], Chris Monten [b], Cai Grau [c], Yolande Lievens [b], Lionel Perrier [d]

[a] Ghent University, European SocieTy for Radiotherapy & Oncology, Brussels; [b] Department of Radiation Oncology, Ghent University Hospital and Ghent University, Belgium; [c] Aarhus University Hospital, Aarhus C, Denmark; [d] Université de Lyon, Léon Bérard Cancer Centre, GATE UMR 5824, Lyon, France

ARTICLE INFO

Article history:
Received 27 May 2019
Received in revised form 13 September 2019
Accepted 23 September 2019
Available online 17 October 2019

Keywords:
Cost evaluation
External beam
Photon beam
Quality
Radiotherapy
Systematic review

ABSTRACT

Purpose/objective: Health economic evaluations (HEE) are increasingly having an impact on policymakers, although the results greatly depend on the quality of the methodology used and on transparent reporting. The two main objectives of this study were to evaluate the quality of cost analyses of external beam radiotherapy (EBRT) and to assess the comprehensiveness and relevance of cost criteria defined in three validated quality-assessment instruments.

Materials and methods: The selection of articles was based on a previous systematic literature review of EBRT-costing studies retrieved from January 2004 to January 2015 (Period 1) in MEDLINE, Embase, and NHS-EED databases and completed in a second time period from January 2015 to November 2018 (Period 2). Three validated instruments to assess the methodology quality with the CHEC and the QHES, and the methodology with the CHEERS checklists were used. The quality was evaluated by both quantitative and qualitative analyses. The scoring robustness was examined with the Kendall coefficient of concordance and inter-class correlation coefficients.

Results: In total, twenty-three articles were selected. The main geographic areas of cost analyses were Canada (n = 5), France (n = 4), and the USA (n = 4). The most commonly studied pathologies and technologies were prostate (n = 7) and head and neck cancer (n = 5) and IMRT (n = 8) and IGRT (n = 2), respectively. The mean instrument scores demonstrated a fair degree of methodological quality, with 69.7% for the CHEC, 73.6% for the QHES, as well as for the reporting quality, with 59.4% for CHEERS for Period 1 (74.4%, 71.5%, and 66.1%, respectively, for Period 2). An additional qualitative analysis per criterion revealed that certain items, essential for understanding the costing methodology and the results (e.g., the time horizon, discount rate, sensitivity analysis) were often only partially completed. Statistical analysis confirmed that the reviewers' scoring was consistent. The instruments identified the same top three articles, albeit with a degree of variation in the ranking.

Conclusion: Qualitative and quantitative assessment of cost analyses in EBRT exhibits a fair level of study quality in terms of the methodology and reporting transparency. The impact of cost calculations on the final HEE result appears to be underestimated, and increased transparency of the data sources and the methodologies is needed.

Health economic evaluations (HEEs) support healthcare policy decision-making by providing information regarding the costs and the consequences of healthcare interventions [1]. In times of limited public resources in conjunction with ever-increasing healthcare expenses, HEEs have become essential to inform policymakers of the acceptability and affordability of new treatments.

This is also the case for radiotherapy: while there is a growing demand due to longer life-expectancies and increasing cancer incidence rates [2], there remains a gap between the availability and the need for radiotherapy [3,4]. In addition, rapid development of more modern radiation oncology treatments, techniques, and technologies has been observed over the past several decades, often resulting in higher costs while also allowing for shorter treatment schedules with higher doses per fraction [5–11]. Hence, more efficient use of radiotherapy resources may compensate for the cost of greater complexity, thereby enabling innovative approaches to be provided to a larger population [12]. Costing studies in the field of radiotherapy are, therefore, needed.

Estimating the cost of radiotherapy can be challenging. Incorrect use of costing terminology is one of the obstacles to fully understand the results of any analysis in healthcare. For example, costs and charges are often used interchangeably, although costs take into consideration longevity as well as use and amortization

* Corresponding author at: Rue Martin V, 40, B-1200 Brussels, Belgium.
E-mail address: ndefourny@estro.org (N. Defourny).

https://doi.org/10.1016/j.radonc.2019.09.020
0167-8140/

of the material, whereas charges are reimbursement-driven [13,14]. Increasingly, reimbursement is chosen as an easy proxy for cost, although reimbursement is based on negotiation with payers and may thus differ not only between countries but even between reimbursement instances [13–15]. For radiotherapy specifically, but also for other specialities requiring large upfront irrecoverable investment in equipment and infrastructure, as is the case for radiotherapy, costing is less straightforward when compared to other domains. Treatment costs are highly dependent on the time needed for treatment delivery and are a composite of costs and time investment of often highly-trained personnel with machine costs and time [10]. There is no standard time of care, as it depends on the treatment indication, the treatment technique, the equipment, and institutional operational parameters. Hence, detailed knowledge of equipment utilization is essential for interpretation of the resulting costs. Such information is rarely described in cost analyses, with the exception of some "time and motion" studies [16]. A last variable, subject to large heterogeneity between departments, is the choice of equipment, with not only differences in the purchase cost, but also for maintenance, amortization, and infrastructure. Such heterogeneity compromises generalizability of the findings to the reader's own situation. [17].

Given the impact that HEEs can have on decisions concerning the allocation of healthcare budgets, such analyses must be methodologically of high-quality and reported in a transparent manner [18,19]. Several qualitative and quantitative checklists have been validated to optimize reporting and/or to appraise HEE methodologies [20,25–27]. These checklists guide authors when writing a comprehensive overview of how results were obtained, and they may assist researchers, reviewers, and editors in selecting articles or in detecting methodological shortcomings [15]. While compliance with guidelines and checklists is a desirable objective, an acceptable quality threshold has yet to be defined [22]. A clear distinction must be made between the quality of the reporting and the quality of the methodology: transparency and completeness are a prerequisite but not a substitute for the quality of an HEE study methodology [21].

Given these existing instruments for assessment of HEE analyses, one could expect a comprehensive evaluation of both clinical and cost components. Checklists should hence allow selective use of the cost criteria to specifically examine the presence of cost components in HEEs. Without transparent reporting, the methodology and data input cannot be evaluated and comprehensively reported.

Previous literature reviews of HEEs of radiotherapy indicate that there is room for improvement [20]. However, the robustness of checklists across readers remains unclear [15,22], especially when applied to cost analyses [24]. Therefore, the first objective of this study was to systematically evaluate the quality of cost analyses in external beam radiotherapy. The second objective was analysis of the consistency of checklists with reviewers of different backgrounds.

Materials and methods

Systematic literature search

In a recent systematic literature review, we searched MEDLINE, Embase, and the National Health Service Economic Evaluation Database (NHS EED) for HEEs of the cost of radiotherapy, published between 1981 and January 2015 [14]. In a second phase, an update of the systematic literature review was carried out for the time period January 2015–November 2018. The search strategy is presented in the Appendix. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. Each of the selected articles was checked in-depth for three additional selection criteria: (i) the subject of the cost calculation had to be external beam radiotherapy; (ii) the costing methodology and the resource inputs had to be reported in detail; (iii) the costs had to be calculated from the hospital perspective. For this assessment, only articles based on original cost analyses and performed since 2005 were included, as this ensured that recent instruments for qualitative economic evaluation were available to the authors.

Quality of the radiotherapy cost studies

Each study was assessed in terms of the methodological and the reporting quality based on three scoring instruments:

- The "Criteria list for assessment of the methodological quality of economic evaluations: Consensus on Health Economic Criteria" (CHEC) [26].
- The "Quality of Health Economic Studies" (QHES) [27].
- The "Consolidated Health Economic Evaluation Reporting Standards" (CHEERS) checklist [20].

The two first checklists were designed to assess methodological quality, while CHEERS are meant to evaluate the reporting quality of HEE analyses. To allow their use for cost analyses, criteria for clinical outcomes are omitted (Appendix).

For the time period January 2005–January 2015 (Period 1), the review was performed by four independent reviewers (CM, JM, ND, and PD), all of whom are experienced in radiotherapy and/or HEE and trained in the proper application of the instruments. As each article was assessed by the three quality appraisal instruments by each of the reviewers, a total of twelve assessments per article were performed. Assessment of the articles retrieved during the update of the initial literature review from January 2015 to November 2018 (Period 2) could only be performed by two of the four original reviewers (CM and ND). For the sake of consistency, both periods cannot be pooled.

The quality of studies analysing the cost of radiotherapy was assessed by a quantitative and a qualitative approach.

Quantitative assessment

As the instruments' assessment methods differ, the creation of a scoring system was necessary to permit comparison of evaluations. We translated the results of the CHEC into a quantitative score, with a correction factor to obtain a total score of 100, thereby allowing comparison with the QHES scale. A similar quantification algorithm was applied for the CHEERS. To ensure scoring transparency, we subdivided criteria covering more than one idea into subcriteria. For the scoring of subcriteria, we applied a binary evaluation system (0 = not present, 1 = present) with the sum of all of the subitems being no more than 1 per item.

The mean quality scores for the two methodology-oriented instruments were compared. The overall scores and the results per quartile for all three scoring instruments are reported. The results were also evaluated based on the year of publication.

Qualitative assessment

Finally, we ran a qualitative analysis of the quality of the selected studies. Through detailed analyses per criterion, we assessed whether the cost criteria as required by the three instruments were addressed in the studies and identified which, if any, criteria were lacking.

Robustness of the instruments' scoring

The consistency of the scoring process was investigated by an interobserver agreement and an interobserver reliability analysis, using a Friedman and a Kendall's coefficient, respectively [28].

While the Friedman two-way rank coefficient evaluates the proximity of reviewer scoring [29], the Kendall correlation coefficient is used to test whether at least one reviewer's score differs [30].

For each checklist, the three most highly ranked articles were defined and compared between the CHEC and the QHES checklists.

Lastly, the intra-class correlation model (ICC) was applied to identify the instrument most independent of reviewers. This test analyses the reliability of instruments by measuring the degree of analytical error (random and systematic) of the scoring while assuming that reviewers are representative of the entire popula-

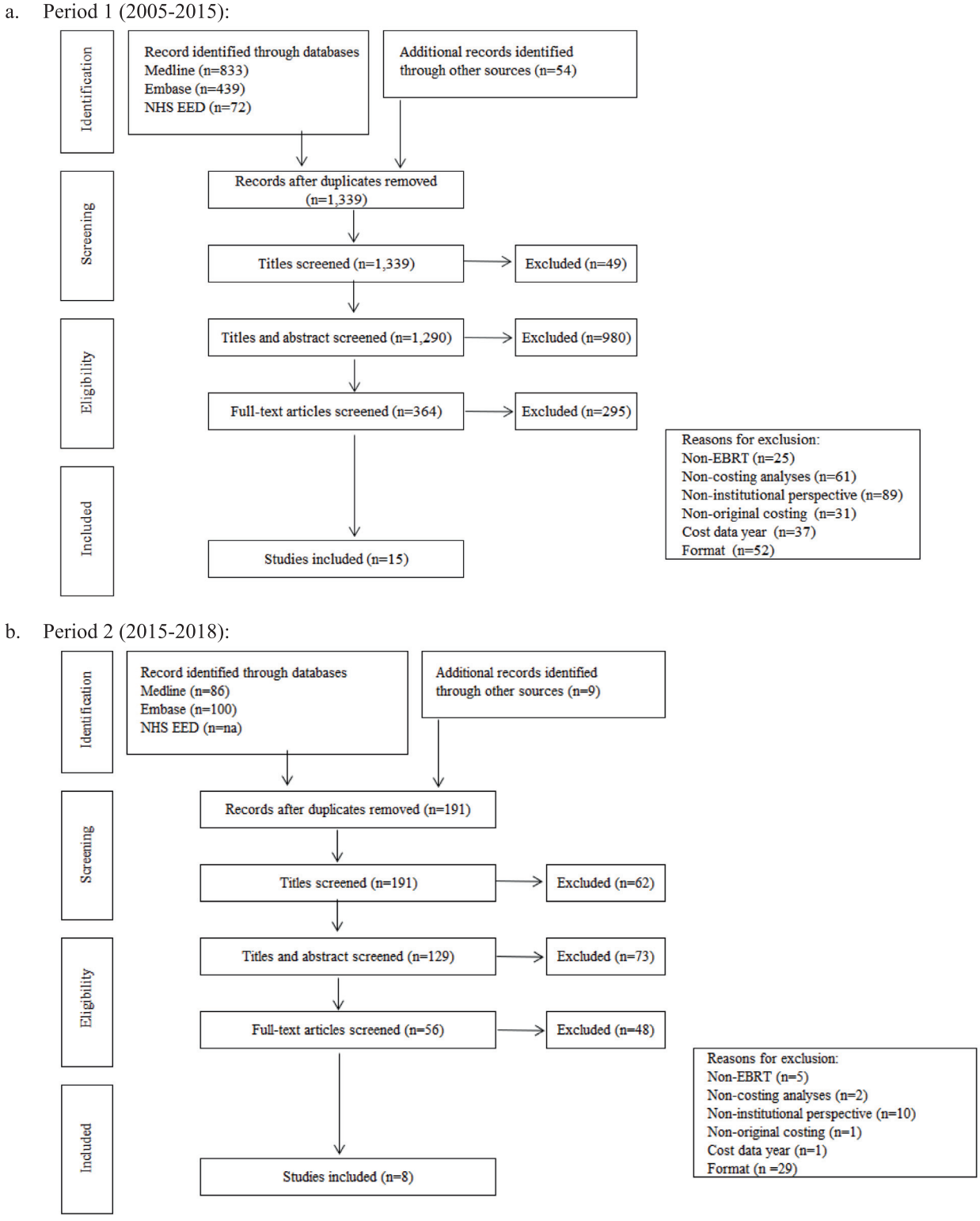

Fig. 1. The preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart showing the record selection process.

tion of evaluators [23,31]. The ICC was preferred as it estimates the magnitude of convergence between a number of non-randomly selected reviewers scoring a fixed number of articles. The robustness of instrument scoring was assessed for Period 1 only. The statistical analysis was conducted using R version 1.1.383 software.

Results

Study selection overview

The initial systematic search identified 1344 references (Period 1). In the second period, 195 references were found, which were reduced to 56 publications after removal of duplicates and by screening titles and abstracts. The main reason for exclusion was the format type, with twenty-three congress proceedings. Ultimately, eight published HEEs were retained. In total, twenty-three articles were selected. The full selection flowchart is presented in Fig. 1.

The study characteristics, design of the cost evaluation, and key results are reported in Table 1. Over the entire period (2005–2018), the main geographical areas of cost analyses were Canada ($n = 5$), France ($n = 4$), and the USA ($n = 4$). The most commonly studied pathologies and technologies were prostate ($n = 7$) and head and neck cancer ($n = 5$) and IMRT ($n = 8$) and IGRT ($n = 2$), respectively. The number of studies in European settings was higher in the second period (France, Belgium, the United Kingdom, the Netherlands, Hungary, Spain, and Ireland).

Sixty-five percent of the selected articles were purely cost analyses. Twenty-six percent also included clinical outcomes with full economic evaluation analyses, mostly cost-effectiveness and cost-utility analyses. Two investment analyses were found. Nine studies were based on a micro-costing method and nine on a (time-driven) activity-based costing methodology. Five did not refer to a specific costing methodology but developed a customized calculation algorithm (Table 1).

Quality of the radiotherapy cost studies

Quantitative assessment

For Period 1, the reporting quality resulted in a mean score of 59.4% (95% CI: 0.56–0.63) for the CHEERS. When a score of 85% was taken to represent "high quality" [35], no study reached this threshold with the CHEERS (Appendix).

The mean scores for the methodological quality of the cost analyses were 69.7% (95% CI: 0.66–0.74) and 73.6% (95% CI: 0.66–0.74) for the CHEC and the QHES, respectively, with a slight degree of variation in the expert scoring ranges (Fig. 2). These results can be considered to represent a fairly good average score [34]. In general, the scores improved slightly over time (Table 2, Fig. 3).

For Period 2, the reporting quality resulted in a mean score of 66.1% (95% CI: 0.59–0.73) for the CHEERS, 74.4% (95% CI: 0.67–0.82) for the CHEC, and 71.5% (95% CI: 0.65–0.78) for the QHES (Table 2).

Qualitative assessment

Detailed analyses per criterion showed that the studies, on average, did not meet one-sixth to one-third of the criteria in both periods (Table 2).

Qualitative examination per criterion highlighted a list of general criteria that were systematically underreported, with, in order of frequency: funding; disclosure of conflict of interest (COI); characterization of uncertainty; discounting, and discussion of the generalizability of the findings. For cost criteria specifically, the following essential items were not addressed in at least 60% of the studies: reporting of the analytical methods used, the time horizon, discounting of future costs, discussion of the magnitude of potential biases, sensitivity analysis, and subgroup analysis (Table 2 and Appendix).

Robustness of the instrument scoring

For all of the checklists, the three highest-ranking scores related to the same top three articles, yet the rank order differed according to each instrument [6,32,33].

Both the Friedman two-way test and the Kendal correlation coefficient demonstrated consistency of scoring between the reviewers, and for all of the instruments. The ICC coefficient exhibited a fair degree of agreement between the reviewers for each instrument, but the level of agreement differed between the instruments, with a concordance of 0.73 (95% CI: 0.523–0.885) for the CHEC, 0.86 (95% CI: 0.725–0.944) for the QHES, and 0.64 (95% CI: 0.401–0.839) for the CHEERS (Table 2).

Discussion

Selected literature on radiotherapy costing and areas of improvement

The number of HEEs evaluating the cost of different radiotherapy techniques or strategies is quite limited. While our review strategy searched for studies with detailed costing analyses, the selection was not restricted to cost analyses only. Cost estimation constituted one of two elements of each cost-effectiveness, cost-utility, or cost-benefit evaluation. Yet only six full HEEs met the criteria for original and detailed reporting of cost-calculations. A potential explanation may be the preference for reimbursement-based costing, which is a strategy often chosen by authors for its simplicity. Moreover, in many of the HEEs, the main focus was on the clinical effectiveness of interventions, at the detriment of transparency regarding the costing methodology as well as resource reporting of the cost-calculation of comparators. Thirdly, most HEEs address findings to payers or governments. Adopting a reimbursement-based methodology provides information regarding the efficiency of their investments. The pitfall, however, lies in the fact that reimbursement levels are negotiated prices, which may overestimate or underestimate the real cost of an intervention. Cost analyses evaluating the real cost of treatment strategies may contribute to alignment of reimbursement with equipment and personnel investment needs.

While Table 1 displays the findings of all the selected studies, interpretation and comparison of the results remains difficult due to the heterogeneity of methodology and the choice of input data as well as due to a recurrent lack of justification of choices. However, through systematic scoring of criteria, several recurrent shortcomings in reporting could be identified (as described in Section 3.2.1, with further details in the Appendix). Most importantly, methodological choices need to be described more systematically and in detail, and a clear time frame should be set to allow interpretation and, if possible, generalization to the particular setting. Comprehensiveness may conflict with word limits in peer-reviewed analyses, but this obstacle can readily be overcome by presenting data information of cost inputs in tables or appendices.

Quality of the radiotherapy cost studies and literature comparisons

The critical assessment of the costing literature in radiotherapy displays a fair standard of quality according to the quartile thresholds approach [34]. These findings fit with the results of previous critical quality assessments of radiotherapy costing analyses conducted by Barbieri et al. [37], Nguyen et al. [22], Becerra et al. [38], and Monten et al. [15]. Barbieri et al. and Nguyen et al. both assessed study quality without computing scores. The qualitative review of Nguyen et al. used a selection of the CHEERS criteria,

Table 1
Characteristics of the 23 studies included in the systematic literature review by chronological order.

Reference	Year	Geographical area, currency	Number of centers	Study population	Interventions being evaluated	Study design	Study perspective	Type of EE	Costing method	Cost valorization year & data collection	Cost discounting rate	Sensitivity analysis	Main cost results
Bonastre [41]	2006	France; €	Multi-center *N* = 9	Oto-rhino-laryngology patients (*N* = 99)	IMRT treatment, 33 fractions on average	RT technique documentation	Hospital	Cost analysis	Micro costing	2001/2, 2003/5	–	–	Mean cost estimation of IMRT treatment is €10,916 (€2773 for planning and €8143 for radiation). Actual reimbursement tariff cover on average for 64% of treatment cost.
Donato [42]	2006	Canada; CAN $	1, *N* = 20	Head and neck (272 images)	2 immobilisation devices: Ultraplast vs. Uvex	Positioning reproducibility	Hospital	Cost Utility Analysis	Micro costing	2004, 2001	Not needed	–	The Ultraplast device provides a field placement reproducibility that is equal to, or greater than, that of the Uvex. Estimation of the immobilization costs per patient are CAN$141.50 and CAN$82.10 for the Uvex' and Ultraplast'
Griffiths [44]	2007	Australia; AU $	1	6 Intracranial lesions	SRS, GK vs. Modified-Linacs	Cost comparison & RT organization	Government perspective	Cost analysis	Unspecified	2005, 2005	5%	Deterministic one-way	The cost per patient on a modified Linac is estimated at AU$3549 vs. AU$3757 on a GK
McJury [48]	2007	United Kingdom; £	1	Head and neck, breast, pelvis, and thorax (*N* = 211 patients)	Conventional simulation vs. virtual	Cost comparison alongside RCT	Hospital	Cost Utility Analysis	Micro costing	2004/5, 2006	–	–	The cost for a 30 fractions treatment with conventional vs. virtual verification for the sites investigated are £1320 and £1316 (£1279 when VS is done during the first fraction); with similar quality of verification
Ploquin [33]	2008	Canada; €	1	21 fractions RT treatment	3D-CRT and IMRT 21 and 35 fractions with EPID, KV, CBCT	Literature cost comparison	Hospital	Cost analysis	ABC	2005, 2005	–	–	From the latest four publications, a 21 fraction RT course cost €3239 ± €566. This is spent on process (54%), clinical (29%) and supporting infrastructure (17%). RT cost increase over the last 15 years is estimated at 5.5%
Nakagawa [49]	2009	Japan; ¥	Multi-center *N* = 8	National RT patients	Carbon ion, proton, BNCT	Cost description	Hospital	Investment analysis	Unspecified	2006, –	–	–	The cost for carbon ion therapy is ¥3.14 million and ¥2.883 million for proton therapy. The cost of BNCT is estimated at a minimum of ¥2.5 million.
Remonnay [5]	2009	France; €	Multi-center, *N* = 8	Lung (NSCLC) and Breast patients (*N* = 365 patients)	Respiratory gating	Cost comparison	Hospital	Cost analysis	Micro costing	2005, 2005	–	–	Respiratory gating routine per treatment costs €996 and €1256 for breath bold in breast and lung while it costs €1510 and €1807, respectively with synchronized gating techniques.
Peeters [45]	2010	The Netherlands; €	1	Dept. patient population	Carbon-ions, protons and photons	Cost comparison	Hospital	Investment analysis	Ad hoc	2007, –	5%	Deterministic one-way	Cost per fraction for photon treatment are estimated at €233 and €743 for proton-only facility. Cost difference for non-small cell lung cancer treatment are relatively small (photon 3DCRT €8150 & SBRT: €3720 vs. proton: €12,380). Cost difference is the largest for head and neck tumours (photon IMRT: €11,520 vs. proton: €39,610)

Table 1 (*continued*)

Reference	Year	Geographical area, currency	Number of centers	Study population	Interventions being evaluated	Study design	Study perspective	Type of EE	Costing method	Cost valorization year & data collection	Cost discounting rate	Sensitivity analysis	Main cost results
Higgins [46]	2010	Canada; CAN $	1	Early stage glottic cancer (T1 or T2)	CO2 laser excision vs. EBRT	Decision-tree model-based EE	Hospital	Cost Effectiveness Analysis	Micro Costing	–	5% at 3 years	Deterministic one-way & two-ways	Radiation cost is CAN€4966/case. Transoral C02 laser excision is dominant over EBRT for this group of patients
Gill [32]	2012	Australia; AU $	1	Prostate	IGRT: KV imaging vs. EPID	Cost minimization	Hospital	Cost Minimization Analysis	Unspecified	2010, 2010	6%	Deterministic multi-ways	The cost per fraction for KVI was AU $258 and for EPI was AU$345. The cost saving per fraction for KVI varied between AU$66 and AU$101
van de Werf [8]	2012	Belgium; €	1	Dept. patient population	RT treatments 2000 vs. 2009	Cost comparison over time	Hospital	Cost description	ABC	2009, 2009	–	–	Average treatment cost of €2,575. The main cost items are : wage (52%), equipment (28.5%), hospital overhead (12.5%). Treatment-related activities (treatment delivery principally) represent 72% of overall costs
Yong [50]	2012	Canada; CAN $	1	Localized prostate cancer	70–80 Gy 3D-CRT vs. IMRT	Cost comparison, Markov model	Hospital	Cost Effectiveness Analysis	TD-ABC	2009, 2005	5%	Deterministic multi-ways	The cost for a prostate treatment with 3D-CRT and IMRT are respectively CAN$13,501 and CAN $14,520, with less frequent gastrointestinal toxicity for the latter
Greenspoon [43]	2013	Canada; CAN $	1	1–3 brain metastases	Robotic vs. Linacs radiosurgery	Incremental cost comparison	Hospital	Cost Benefit Analysis	Ad hoc	2009, 2009	5%	–	The yearly cost of providing robotic radiosurgery is CAN$635,041 and CAN$535,864 for fixed gantry radiosurgery
Hulstaert [47]	2013	Belgium; €	Multi-center $N = 10$	Curative Prostate; Lung; Breast treatments	IMRT 33–40 fractions; 3D hypo-fractionated; 12–20 with and without boost	Cost description	Hospital	Cost analysis	ABC	2011, 2011/2	–	Deterministic one-way	For lung cancer, the average cost of SBRT (€6221) is in the range of the average costs of standard fractionated 3DCRT (€5919) and IMRT (€7379). Hypo fractionated 3DCRT and IMRT schemes are less costly (€3993 respectively €4730)
Perrier [6]	2013	France; €	Multiple $N = 5$	Prostate cancer ($N = 208$ patients)	Image-guided RT	Cost comparison alongside RCT	Hospital	Cost analysis	Micro costing	2009, 2007/11	–	Deterministic multi-ways, probabilistic nonparametric bootstrap	The mean additional cost per patient of daily controls compared with weekly controls was €679 and €187 for CBCT and EPI-FM, respectively
Hanly [51]	2015	Ireland; €	2	Rectal cancer	25 fractions vs. 5 fractions	Cost comparison	Hospital	Cost analysis	Micro costing	2012, 2010–2011	4%	Sensitivity analysis	For rectal cancer, the cost of a typical treatment cost is estimated between €2080 (5 fractions courses) and €3609 (25 fractions course). Cost per fractions is respectively 154€ and 92€. The scenario analysis shows that an efficient treatment time would decrease cost by respectively, 35% and 20%. When the assumed 100% capacity utilization is relaxed to simulate an extension of service hours to 125%, the cost per courses falls up to 25%
Laviana [52]	2016	USA; US$	1	Localized prostate cancer	IMRT vs. SBRT	Cost comparison	Hospital	Cost analysis	TD-ABC	–, 2013/15	–	–	The cost of prostate treatment is estimated through 5 years of follow-up, resulting in cost ranging

(*continued on next page*)

Table 1 (*continued*)

Reference	Year	Geographical area, currency	Number of centers	Study population	Interventions being evaluated	Study design	Study perspective	Type of EE	Costing method	Cost valorization year & data collection	Cost discounting rate	Sensitivity analysis	Main cost results
													from $7289 for active surveillance, $11,665 for SBRT and $23,565 for IMRT. Cost per treatment session was $479 for SBRT and $298 for IMRT). At 1 year of follow-up, SBRT ($10,632) and IMRT ($22,532) costs are similar to those reported by other using Medicare claims
Perrier [54]	2016	France; €	14	Head and neck cancer	TomoTherapy © vs. RapidArc ©	Cost comparison alongside RCT	Hospital	Cost analysis	Micro costing	2013	–	Deterministic multi-ways	Mean costs per patient for planning session is estimated at €314 (SD: ±€214) for TomoTherapy and €511 (SD: ±€590) for RapidArc. The treatment sessions were on average, respectively €3144 (SD: ±€565) and €1350 (SD: ±€299). This difference is mainly due to higher acquisition price, maintenance costs and longer duration of treatment session
Schutzer [55]	2016	USA; US$	1	Early stage breast cancer	Whole-breast RT vs. accelerated partial-breast irradiation	Cost comparison	Hospital	Cost analysis	TD-ABC	–	–	–	Total cost for WBRT is estimated at $5333 for conventional fractionation, at $4074 for hypofractionation and, at $6941 for APBI. The cost per session is $246 for conventional treatment fractionation. The main cost item is personnel cost making up respectively, 56% and 51% of total costs
van Dyk [56]	2017	Income-regions; US$	Model	Typical RT treatment	50/50 3D-CRT/IMRT 19.4 fractions	Cost comparison across regions	Hospital	Cost analysis	TD-ABC	Not applicable	–	Scenario analysis / Deterministic one-way	The cost of a typical RT treatment is US$5368 in high-income countries (HICs) and US$2028 in low-income countries (LICs). The annual operating cost is respectively, US $4,595,000 and US$1,736,000. The use of IMRT technique increase treatments cost by 22% in both HICs and LICs. In terms of economies of scale, the cost per course decreases with increasing department size, mainly related to the equipment cost and most prominent up to 3 Linacs
Bauer-Nilsen [57]	2018	USA; US$	1	Locally advanced cervical cancer	50/50 3D-CRT/IMRT 25 fractions	Cost comparison	Hospital	Cost analysis	TD-ABC	2016, –	–	–	For cervical cancer, cost of a RT treatment is estimated at $12,861.68, with personnel costs constituting 49.8%. The reimbursement tariffs exceed the delivery cost for both 3D-CRT and IMRT

Table 1 (*continued*)

Reference	Year	Geographical area, currency	Number of centers	Study population	Interventions being evaluated	Study design	Study perspective	Type of EE	Costing method	Cost valorization year & data collection	Cost discounting rate	Sensitivity analysis	Main cost results
Zemplenyi [58]	2018	Hungary; €	1	Localized prostate cancer	3D-CRT 35–39 fractions; IMRT 37–40 fractions; IMRT hypofractionation of 25 fractions	Cost comparison, Markov model	Hospital	Cost Effectiveness Analysis	Micro costing	2014, –	3.7%	Probabilistic sensitivity analysis	The cost 3DCRT, IMRT and hypofractionated IMRT treatments were 2105€, 3066€ and 2244€ respectively. Additional (sensitivity) analysis using reimbursements demonstrates cost-effectiveness of the novel IMRT therapies, with currently equal tariff of 3648€ for 3D-CRT and IMRT treatment and, a lower one of 2769€ for hypofractionated IMRT treatment
Dutta [59]	2018	USA; US$	1	Prostate cancer	IMRT: 28 fractions vs. 39 fractions.	Cost comparison	Hospital	Cost analysis	TD-ABC	2016, –	–	–	The cost estimated for a moderately hypofractionated 28-fraction IMRT is $4173, $5507 for a conventionally fractionated 39-fraction IMRT and $10,377 for a conventionally fractionated 23-fraction pelvis irradiation with 16-fraction prostate boost

Note:
Societal perspective: are only displayed if cost results of the health care provider perspective are displayed distinctly.
3D-CRT, Three-dimensional conformational Radiotherapy
Ad hoc, Costing category label for study displaying an exhaustive and detailed description of the calculation algorithm including assumptions and data sources.
BT, Brachytherapy.
BNCT, Boron Neutron Capture Therapy.
CBCT, Cone Beam CT.
Chart, Continuous Hyperfractionated Accelerated Radiotherapy.
CT, Chemotherapy.
CS, Conventional simulation.
Dept., Department.
EBRT, External Beam Radiotherapy.
EPID, Electronic Portal Imaging Device.
GK, Gama Knife.
Gy, Gray.
H&N, Head and Neck.
IMRT, Intensity-modulated Radiotherapy.
KV, Kilo voltage image.
LSP, Lumbosacral Plexus.
ND, Neck Dissection.
NSCLCvNon-small cell lung cancer.
RT, Radiotherapy.
SD, Standard Deviation.
SRS, Stereotactic Radiosurgery.
SRT, Stereotactic Radiotherapy.
TLD, Thermoluminescent Dosimeter.
vs., Versus.

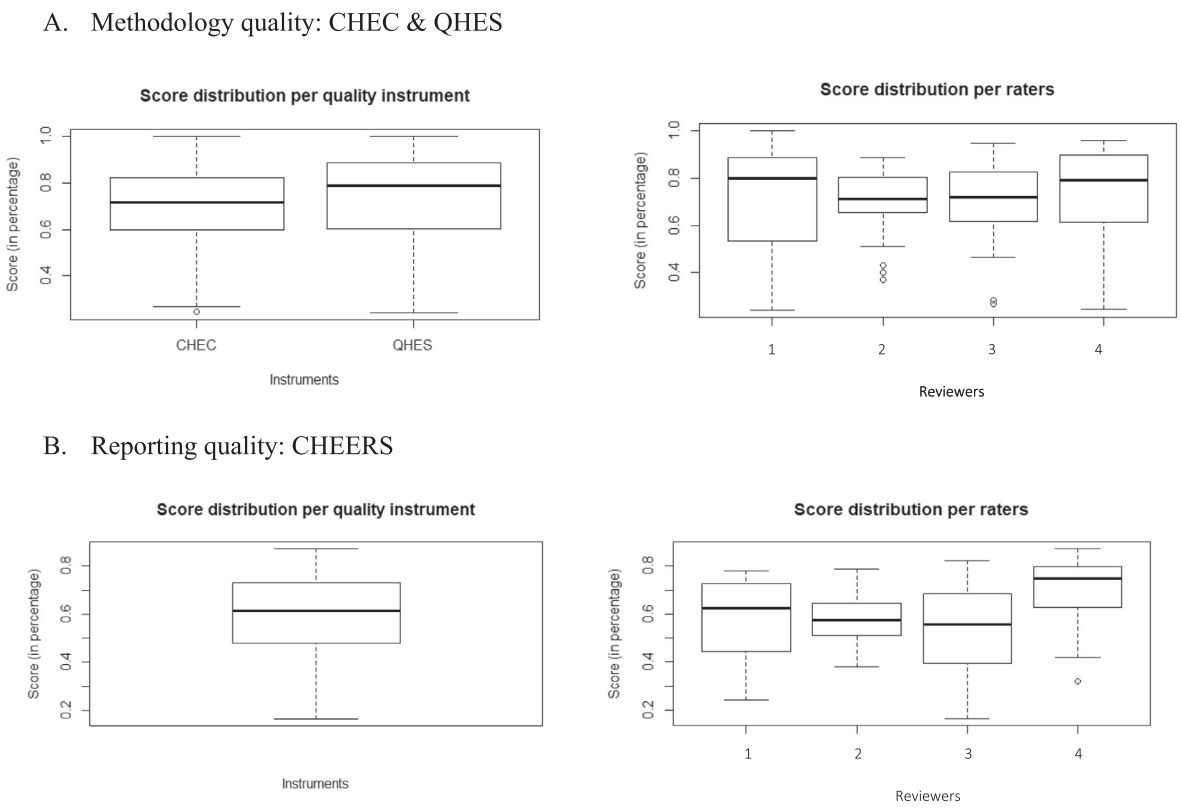

Fig 2. The quality scores of articles per instrument (left) and per reviewer (right) for the initial round (Period 1) of the literature selection. Methodology quality: CHEC & QHES.

whereas Barbieri et al. made use of the NICE and the Drummond checklists [39,40]. The study by Barbieri et al. limited the assessment to UK-specific method requirements (e.g., a discount of 3.5%), which may explain the low ratio of compliance of the HEEs they found [37]. Nguyen et al. observed an improvement in the reporting for some of the criteria (declaration of conflict of interest and the presence of multivariate sensitivity analyses) in studies published after 2010.

Similar to Barbieri, Becerra et al. assessed the literature on localized prostate cancer treatment according to the Drummond checklist without any quantitative synthesis of the results. The large cost differences found (mainly from the healthcare payer perspective) suggests an underestimation of cost estimates from theoretical cohorts compared to empirical ones.

Focusing on HEEs of breast RT as a subgroup, Monten et al. found a higher score for the CHEERS, at (75.6%, CI: 70.7–80.5%), than in the present study, while the score of the QHES was similar to ours (75.2%, CI: 67.8–82.6%). This difference can probably be explained by the choice to subdivide into subcriteria in the present study. Another advantage of this study is the higher number of reviewers.

Complementarity between the quality instruments

Previous interpretation of the ICC results suggested the use of 0.8 as the threshold for excellent agreement [36]. This would mean that our results have an acceptable to high-level of interobserver agreement. Differences between the reliability of instruments may be explained by characteristics of the checklists. A higher number of criteria may enhance specificity, but this comes with a risk of increased interobserver disagreement. The number of requested criteria is often masked through pooling or grouping of several subcriteria within one question. This strategy may further add to divergence as it allows reviewers to apply either a severe scoring ('not fulfilled' if the minimal requirements are missing), a very generous rating ('complete' if at least one requirement is present), or anything in between. This pitfall – reported previously [23] – has been avoided in our assessment by subdividing each criterion into subcriteria, revealing that the CHEERS checklist contains more than twice the number of subcriteria than the other two checklists.

The high number of subcriteria (50 in total) may explain why we found the lowest ICC score for the CHEERS, despite it not evaluating the quality of the methodology. This observation fits with an earlier study that identified the number of criteria per instrument as a source of measurement error [24]. However, the number of subcriteria is probably not sufficient to explain the difference between the CHEC (25 subcriteria) and the QHES (21 subcriteria). A complementary factor contributing to the interobserver disagreement may have been the large proportion of "opinion-type criteria" in the CHEC compared to the QHES. Three types of questions can be discerned in the analysed checklists. Listed from least to most prone to subjectivity, these types are: (1) the "factual type", which records the presence or the absence of one specific type of information, (2) the "justification type", which indicates whether the choice is motivated, (3) the "opinion type", which requires an interpretation or judgment of the choices made. Whereas the QHES mainly rates the presence of reporting factors, the CHEC contains more systematically open questions on the justification and appropriateness of the chosen methodology Although this strategy broadens the scope by adding a perspective on the quality of the economic evaluation performed, it does increase the subjectivity. Ambiguity could have been avoided by more clearly defining what is expected. An example may be found in criterion 8a of the QHES, where discounting only needs to be present if costs go beyond 1 year and where discounting should

Table 2
Results of statistical and descriptive analysis.

Instruments scope	Methodological Quality:		Reporting Quality:
	CHEC [26]	QHES [27]	CHEERS [20]
I. Quantitative assessment			
a. Period 1 (4 raters):			
Mean (SD) *Confidence interval*	69.7% (0.150) *61.5–78.2%*	73.6% (0.179) *63.7–83.5%*	59.4% (0.139) *52.3–68.3%*
Per quartiles[a]**:** percentage of studies (n)			
75–100	53.3% (8)	53.3% (9)	6.6% (1)
50–74	33.3% (5)	33.3% (5)	66.6% (10)
25–49	13.3% (2)	13.3% (2)	26.6% (4)
0–24	–	–	–
Per year of publication: mean score			
2006 (n = 2)	0.51	0.51	0.42
2007 (n = 3)	0.74	0.78	0.63
2009 (n = 2)	0.51	0.55	0.44
2010 (n = 2)	0.83	0.88	0.65
2012 (n = 3)	0.74	0.81	0.65
2013 (n = 3)	0.78	0.79	0.69
b. Period 2 (2 raters):			
Mean (SD) *Confidence interval*	74.4% (0.143) *66.8–82.1%*	71.5% (0.130) *64.6–78.4%*	66.1% (0.131) *59.1–73%*
Per quartiles[a]**:** percentage of studies (n)			
75–100	92% (2)	83% (3)	82% (2)
50–74	69% (6)	65% (5)	62% (6)
25–49	–	–	–
0–24	–	–	–
Per year of publication: mean score			
2015 (n = 1)	68%	77%	74%
2016 (n = 2)	73%	72%	66%
2017 (n = 1)	74%	62%	65%
2018 (n = 3)	78%	72%	64%
II. Qualitative assessment			
Percentage of unmet criterion			
a. Period 1 (4 raters):	21%	18.5%	29.6%
b. Period 2 (2 raters):	20%	16%	30%
Per criterion[b]: percentage (n[c]) of **full** criterion endorsement			
a. Period 1 (4 raters):			
1	80% *(48)*	88% (53)	80% (48)
2	95% (57)	48% (29)	70% (42)
3	35% (39)	NA	82% (49)
4	90% (21)	58% (35)	37% (22)
5	42% (25)	50% (30)	90% (54)
6	88% (53)	67% (40)	75% (45)
7	85% (51)	NA	83% (50)
8	33% (20)	28% (17)	35% (21)
9	NA	78% (47)	28% (17)
10	NA	NA	NA
11	NA	NA	NA
12	67% (40)	77% (46)	NA
13	30% (18)	55% (33)	A: 45% (25), B: 7% (4)
14	55% (33)	37% (22)	22% (13)
15	93% (56)	87% (52)	57% (34)
16	47% (28)	47% (28)	73% (44)
17	38% (23)	–	48% (29)
18	37% (22)	–	23% (14)
19	–	–	57% (34)
20	–	–	A: 22% (13), B: 12% (7)
21	–	–	35% (21)
22	–	–	43% (26)
23	–	–	47% (28)
24	–	–	28% (17)
b. Period 2 (2 raters):			
1	100% *(16)*	100% *(16)*	50% *(8)*
2	100% *(16)*	63% *(10)*	94% *(15)*
3	69% *(11)*	NA	88% *()*14
4	31% *(5)*	100% *(16)*	44% *(7)*
5	69% *(11)*	44% *(7)*	94% *(15)*
6	75% *(12)*	69% *(11)*	94% *(15)*
7	75% *(12)*	NA	81% *(13)*
8	38% *(6)*	13% *(2)*	25% *(4)*
9	NA	38% *(6)*	19% *(3)*
10	NA	NA	NA

(*continued on next page*)

Table 2 (*continued*)

Instruments scope	Methodological Quality:		Reporting Quality:
	CHEC [26]	QHES [27]	CHEERS [20]
11	NA	NA	NA
12	63% *(10)*	44% *(7)*	NA
13	13% *(2)*	50% *(8)*	A: 19% (3), B: 6% (1)
14	44% *(7)*	63% *(10)*	0% *(0)*
15	100% *(16)*	100% *(16)*	56% *(9)*
16	100% *(16)*	75% *(12)*	69% *(11)*
17	100% *(16)*	–	56% *(9)*
18	63% *(10)*	–	13% *(2)*
19	–	–	44% *(7)*
20	–	–	A: 19% (3), B: 25% (4)
21	–	–	31% *(5)*
22	–	–	94% *(15)*
23	–	–	63% *(10)*
24	–	–	88% *(14)*
III. Statistical robustness of quantitative assessment for period 1IV			
Kendall's coefficient of concordance (subjects = 15, raters = 4): w *(p-value)*	0.783***	0.887***	0.72***
Friedman two ways (df = 3): Chi-squared *(p-value)*	1.0227*(0.7958)*	0.29032 (*0.9618*)	0.41007 (*0.9382*)
Agreement ICC (A,1), p-value	0.732***	0.859***	0.641***
Confidence interval	*0.523–0.885*	*0.725–0.944*	*0.401–0.839*

***Significative at 1%; **Significative at 5%; *Significative at 10%.

[a] Thresholds are based on the following publications [34,35].

[b] The criterion refers to the numbering of each instrument, hence it does not cover identical components (see Appendix).

[c] The number of articles in which reviewers' scores observed the presence of these criteria. The total score sums up to 60, based on 15 articles scored by 4 reviewers.

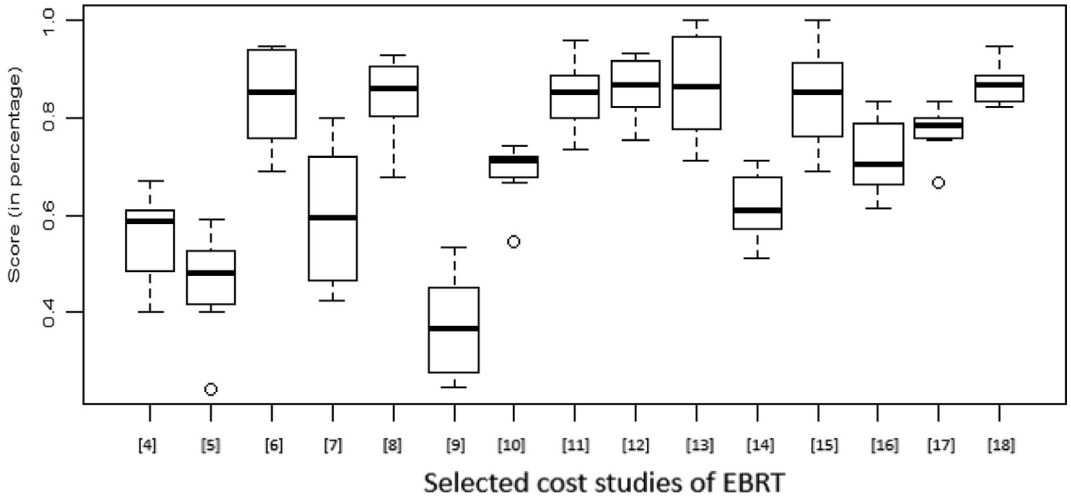

Fig 3. Change of selected articles over time: quality scores for the CHEC and the QHES for the initial round (Period 1) of the literature selection.

be a factor between 3 and 5%. This argument confirms the findings of Gerkens et al. [23], who indicated how, apart from the time spent by and the experience of observers with HEE assessment, the most important cause of disagreement was the ambiguity in the interpretation of criteria. A robust checklist should avoid ambiguous and subjective questions to become independent of the reviewers' profile.

Although our quantitative results indicate acceptable performance of the instruments, the qualitative analysis does reveal specific shortcomings. Focusing on the cost-criteria of the instruments, we found a slightly different relative weight of costing criteria between studies, with 43% of the score determined by costing criteria for the CHEC versus 34% for the QHES, while it was 28% for the CHEERS. Several specific economic components essential for cost calculations are lacking from all three instruments. For example, none of the instruments requests identification of the cost system applied. Hence, no distinction between a conventional costing methodology such as time-driven activity-based costing or micro-costing, versus 'ad hoc' methodologies can be made. Moreover, costs may differ substantially, depending on the components that are taken into consideration, e.g., resource utilization rates, overhead composition and allocation rules, and attribution of idle resource time versus full capacity assumption. Restrictions regarding the number of words in most journal articles may lead to selection of the data reported. However, this obstacle can readily be overcome by adding a detailed overview of the input data and the methodology as an appendix, or by applying a conventional methodology that can be cited. Transparency on the economic components is essential for evaluation of generalizability to one's context: in contrast to clinical outcomes, costs are determined by organizational and financing structures, which are specific to countries and departments. With comprehensive descriptions, the reader is offered the opportunity to compare cost components with their own situation. This finding correlates with the observation that the discussion of generalizability of cost-findings to their contexts warrants a more extensive discussion in most HEEs.

Strengths and limitations

The use of multiple instruments, each with its specific asset, provides broad insight into the quality of the RT studies reviewed. The number of reviewers, all experienced in HEE, provides a strong and original sample for this evaluation, as recommended by Gerkens et al. [23]. Moreover, the division of criteria into single-component items reduces interpretation of the scoring system by reviewers, while enhancing granularity and transparency of the evaluation. Additionally, while the inclusion of publications outside the peer-review literature is indispensable to capture reports from Health Technology Assessment institutes, it adds a positive bias to this assessment.

However, limiting the available instruments to the appraisal of cost analysis only by removing clinical effectiveness criteria, may have affected the validity of these checklists [53]. Moreover, the transformation of qualitative checklists into quantitative instruments has not yet been validated for the CHEC and the CHEERS. The QHES quantitative approach assigns different weights to different criteria, resulting in a score of 100 points. The same total score results from the quantification algorithm for both the CHEC and the CHEERS [35]. In contrast to the QHES, however, a uniform weight is assigned to each criterion, independently of its relevance. As a result, the weight per criterion, and thus its importance, differs between the checklists. Whereas quantification allows benchmarking, the optimal methodology remains to be defined.

While the quantitative analysis could not be performed on the studies published after 2015, the overall scores indicated a slight improvement when compared with the publications up to 2015.

Conclusions

Qualitative and quantitative assessments of cost analyses in external beam radiotherapy exhibit a fair degree of study quality in terms of methodology and reporting transparency.

However, more comprehensive reporting on the methodology, the time frames, and the cost input data may improve the validity and the acceptability of HEE results. The impact of cost calculations on the final HEE result appears to be underestimated, and increased transparency of data sources and methodologies is needed. The robustness of checklists may be improved by being restricted to one idea per criterion, by avoiding opinion type questions and, if inevitable, by clearly defining what is expected if an evaluation of "appropriateness" is requested. Where quantification of quality assessment results facilitates benchmarking, this should always be completed with a qualitative analysis to reveal shortcomings of components that are essential to obtain reliable results.

Author contributions

LP, YL, PD, and ND contributed to the study rationale and design and they performed a systematic review and quality assessment of the identified studies. CM, JM, ND, and PD conducted the critical assessment of the studies. JM, CM, and ND carried out the interpretation of the data. ND and CM drafted the manuscript, and all of the authors revised it critically in regard to its main intellectual content and they approved the final version submitted for publication.

Funding

This study was independent research funded by the European SocieTy for Radiotherapy and Oncology (ESTRO) as part of the HERO Programme for travel to meetings. The views expressed in the publication are those of the authors and not necessarily those of the ESTRO.

Declaration of Competing Interest

CM, CG, YL, and LP declare that they have no conflicts of interest.

ND declares being employed by ESTRO in the context of a PhD program.

Acknowledgements

We thank DUNSCOMBE Peter (Deceased Emeritus Professor, Calgary University, Canada) and MONNET Julia (Lyon Cancer Institute, France) for their contributions to this research and Chiara Gasparotto (ESTRO, Rue Martin V, 40; B-1200 Brussels, Belgium) for her revisions. Dr. Sophie Domingues-Montanari Scientific and Medical Translation (Barcelona, Spain) assisted with the final editing of the manuscript. The authors also thank the reviewers for their valuable comments.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.09.020.

References

[1] Niessen LW, Bridges J, Lau BD et al. Assessing the impact of economic evidence on policymakers in health care—a systematic review. 2012 Methods Research Report (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract No. 290-2007-10061-I). AHRQ Publication No. 12(13)-EHC133-EF. Rockville, MD: Agency for Healthcare Research and Quality https://www.ncbi.nlm.nih.gov/books/NBK114636/?report=printable [Accessed 13 March 2018].
[2] Borras J, Lievens Y, Barton M, et al. How many new cancer patients in Europe will require radiotherapy by 2025? An ESTRO-HERO analysis. Radiother Oncol. 2016;119:5–11.
[3] Borras J, Lievens Y, Dunscombe P, et al. The optimal utilization proportion of external beam radiotherapy in European countries: an ESTRO-HERO analysis. Radiother Oncol 2015;116:38–44.
[4] Atun R, Jaffray D, Barton M, et al. Expanding global access to radiotherapy. Lancet Oncol 2015;16:1153–86.
[5] Remonnay R, Morelle M, Giraud P, Carrere M-O. The cost of respiration-gated radiotherapy in the framework of a clinical research programme "STIC". Cancer/Radiotherapie 2009;13:281–90.
[6] Perrier L, Morelle M, Pommier P, et al. Cost of prostate image-guided radiation therapy: results of randomized trial. Radiother Oncol 2013;106:50–8.
[7] Berkovic P, Paelinck L, Gulyban A, et al. Adaptive radiotherapy for locally advanced non-small cell lung cancer: dosimetric gain and treatment outcome prediction. Acta Oncol 2017;56(11):1656–9.
[8] van de Werf E, Verstraete J, Lievens Y. The cost of radiotherapy in a decade of technology evolution. Radiother Oncol 2012;102:148–53.
[9] Lievens Y. Hypofractionated breast radiotherapy: financial and economic consequences. The Breast 2010;19(3):192–7.
[10] Lievens Y, Obyn C, Mertens AS, Van Halewyck D, Hulstaert F. Stereotactic body radiotherapy for lung cancer: how much does it really cost?. JTO 2015;10 (3):454–61.
[11] Monten C, Lievens Y. Adjuvant breast radiotherapy: how to trade-off cost and effectiveness?. Radiother Oncol 2018;126(1):132–8.
[12] Van Dyk J, Zubizarreta E, Lievens Y. Cost evaluation to optimise radiation therapy implementation in different income settings: a time-driven activity-based analysis. Radiother Oncol 2017;125(2):178–85. https://doi.org/10.1016/j.radonc.2017.08.021.
[13] Kaplan R, Porter M. How to solve the cost crisis in health care?. Harvard Bus Rev 2011;9:47–64.
[14] Defourny N, Dunscombe P, Perrier L, Grau C, Lievens Y. Cost evaluations of radiotherapy: what do we know? An ESTRO-HERO analysis. Radiother Oncol 2016;121(3):468–74.
[15] Monten C, Veldeman L, Verhaeghe N, Lievens Y. A systematic review of health economic evaluation in adjuvant breast radiotherapy: quality counted by numbers. Radiother Oncol 2017;125(2):186–92.
[16] Beech R, Burgess K, Stratford J. Process evaluation of treatment times in a large radiotherapy department. Radiography 2016;22:206–16.
[17] Wordsworth S, Ludbrook A, Caskey F, Macleod A. Eur J Health EconN 2005:38–44.
[18] Langer A. A framework for assessing Health Economic Evaluation (HEE) quality appraisal instruments. BMC Health Services Res 2012;12(1):253.
[19] Lievens Y, Borras J, Grau C. Cost calculation, a necessary step towards widespread adoption of advanced radiotherapy technology. Acta Oncol 2015;54:1275–81.

[20] Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: a report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231–50.
[21] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force–7. Med Decis Making 2012;32(5):733–43.
[22] Nguyen TN, Goodman CD, Boldt RG, et al. Evaluations of health economics in radiation oncology: a systematic review. Int J Radiat Oncol Biol Phys 2016;94:1006–14.
[23] Gerkens S, Crott R, Cleemput I, et al. Comparison of three instruments assessing the quality of economic evaluations: a practical exercise on economic evaluations of the surgical treatment of obesity. Int J Technol Assess Health Care 2008;24(3):318–25.
[24] Au F, Prahardhi S, Shiell A. Reliability of two instruments for critical assessment of economic evaluations. Value Health 2008;11(3):435–9.
[25] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. BMJ 1996;313:275–83.
[26] Evers S, Goossens M, De Vet H, Van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: consensus on Health Economic Criteria. Int J Technol Assess Health Care 2005;21(2):240–5.
[27] Chiou CF et al. Development and validation of a grading system for the quality of cost-effectiveness studies. Med Care 2003;32–44.
[28] Hallgren KA. Computing inter-rater reliability for observational data: an overview and tutorial. Tutor Quant Methods Psychol 2012;8(1):23.
[29] Legendre P. Coefficient of concordance. Encyclopedia Res. Des. 2010;1:164–9.
[30] Chaturvedi SRBH. Evaluation of inter-rater agreement and inter-rater reliability for observational data: an overview of concepts and methods. J Indian Acad Appl Psychol 2015;41(3):20–7.
[31] Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86(2):420.
[32] Gill S, Younie S, Rolfo A, et al. Cost minimisation analysis: kilovoltage imaging with automated repositioning versus electronic portal imaging in image-guided radiotherapy for prostate cancer. Clin Oncol 2012;24:e93–9.
[33] Ploquin N, Dunscombe P. The cost of radiation therapy. Radiother Oncol 2008;86:217–23.
[34] Spiegel BM, Targownik LE, Kanwal F, et al. The quality of published health economic analyses in digestive diseases: a systematic review and quantitative appraisal. Gastroenterology 2004;127(2):403–11.
[35] Plumpton CO, Roberts D, Pirmohamed M, Hughes DA. A systematic review of economic evaluations of pharmacogenetic testing for prevention of adverse drug reactions. Pharmacoeconomics 2016;34:771–93.
[36] Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[37] Barbieri M, Weatherly H, Basarir H, et al. What is the quality of economic evaluations of non-drug therapies? A systematic review and critical appraisal of economic evaluations of radiotherapy for cancer. Appl Health Econ Health Policy 2014;12:497–510.
[38] Becerra V, Avila M, Jimenez J, et al. Economic evaluation of treatments for patients with localized prostate cancer in Europe: a systematic review. BMC Health Serv Res 2016;16(1):541.
[39] National Institute for Health and Clinical Excellence (NICE). Guide to the Methods of Technology Appraisals 2008. http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf [Accessed 2 May 2017].
[40] Drummond MF. Methods for the economic evaluation of health care programmes. 3rd ed. Oxford: Oxford University Press; 2005.
[41] Bonastre MJ, Noël E, Bensadoun RJ, et al. The cost of intensity modulated radiation therapy in head and neck cancers: results of the 2002 STIC study. Bull Cancer 2006;93:1026–32.
[42] Donato K, Leszczynski K, Fleming K. A comparative evaluation of two head and neck immobilization devices using electronic portal imaging. Brit J Radiol 2006;79:158–61.
[43] Greenspoon JN, Whitton A, Whelan T, et al. Robotic radiosurgery for the treatment of 1–3 brain metastases: a pragmatic application of cost-benefit analysis using willingness-to-pay. Technol Cancer Res Treat 2013;12:517–23.
[44] Griffiths A, Marinovich L, Barton MB, Lord SJ. Cost analysis of Gamma Knife stereotactic radiosurgery. Int J Technol Assess Health Care 2007;23:488–94.
[45] Peeters A, Grutters JP, Pijls-Johannesma M, et al. How costly is particle therapy? Cost analysis of external beam radiotherapy with carbon-ions, protons and photons. Radiother Oncol 2010;95:45–53.
[46] Higgins K. What treatment for early-stage glottic carcinoma among adult patients: CO2 endolaryngeal laser excision versus standard fractionated external beam radiation is superior in terms of cost utility?. Laryngoscope 2011;121:116–34.
[47] Hulstaert F, Mertens AS, Obyn C, et al. Innovative radiotherapy techniques: a multicentre time-driven activity-based costing study. Health Technology Assessment (HTA) Brussels: Belgian Health Care Knowledge Centre (KCE). 2013; KCE Reports 198C. D/2013/10.273/9 [Accessed 10 Nov 2014].
[48] McJury M, Foran B, Conway J, et al. Optimising the use of virtual and conventional simulation: a clinical and economic analysis. J Radiother Pract 2007;6:83–91.
[49] Nakagawa Y, Yoshihara H, Kageji T, Matsuoka R. Cost analysis of radiotherapy, carbon ion therapy, proton therapy and BNCT in Japan. Appl Radiat Isot 2009;67:s80–3.
[50] Yong JH, Beca J, O'Sullivan B, et al. Cost-effectiveness of intensity-modulated radiotherapy in oropharyngeal cancer. Clin Oncol 2012;30:532–8.
[51] Hanly P, Céilleachair AÓ, Skally M, O'Neill C, Sharp L. Direct costs of radiotherapy for rectal cancer: a microcosting study. BMC Health Serv Res 2015;15:184.
[52] Laviana AA, Ilg AM, Veruttipong D, et al. Utilizing time-driven activity-based costing to understand the short-and long-term costs of treating localized, low-risk prostate cancer. Cancer 2016;122:447–55.
[53] Sharieff W, Greenspoon JN, Dayes I, et al. The technique, resources and costs of stereotactic body radiotherapy of prostate cancer: a comparison of dose regimens and delivery systems. Technol Cancer Res Treat 2016;15:171–8.
[54] Perrier L, Morelle M, Pommier P, et al. Cost analysis of complex radiation therapy for patients with head and neck cancer. Int J Radiat Oncol Biol Phys 2016;95:654–62.
[55] Schutzer ME, Arthur DW, Anscher MS. Time-driven activity-based costing: a comparative cost analysis of whole-breast radiotherapy versus balloon-based brachytherapy in the management of early-stage breast cancer. J Oncol Pract 2016;12:e584–93.
[56] Van Dyk J, Zubizarreta E, Lievens Y. Cost evaluation to optimise radiation therapy implementation in different income settings: a time-driven activity-based analysis. Radiother Oncol 2017;125(2):178–85.
[57] Bauer-Nilsen K, Hill C, Trifiletti DM, et al. Evaluation of delivery costs for external beam radiation therapy and brachytherapy for locally advanced cervical cancer using time-driven activity-based costing. Int J Radiat Oncol Biol Phys 2018;100(1):88–94.
[58] Zemplenyi AT, Kalo Z, Kovacs G, et al. Cost-effectiveness analysis of intensity-modulated radiation therapy with normal and hypofractionated schemes for the treatment of localised prostate cancer. Eur J Cancer Care 2018;27(1):e12430.
[59] Dutta SW, Bauer-Nilsen K, Sanders JC, et al. Time-driven activity-based cost comparison of prostate cancer brachytherapy and intensity-modulated radiation therapy. Brachytherapy 2018;17(3):556–63.