Evaluation of novel radiotherapy technologies: what evidence is needed to assess their clinical and cost effectiveness, and how should we get it?

Judith van Loon, Janneke Grutters, Fergus Macbeth

Technical innovations in radiation oncology—eg, intensity-modulated radiotherapy, stereotactic radiotherapy, and particle therapy—can be developed rapidly and introduced into the clinic even when costs associated with their use are much higher than those for conventional radiotherapy. Although clinical benefit is expected on the basis of superior biological and physical characteristics, data for clinical effectiveness of new radiotherapy techniques are scarce. Evidence from randomised clinical trials would be ideal but such studies focus mostly on new drugs. High investment costs and modifications over time make evaluation of novel radiotherapy technologies in clinical trials more complex. Here, we propose an algorithm for evaluation of the clinical and cost effectiveness of novel radiotherapy technologies. We suggest situations when randomised trials might be feasible and the type of trial that should be undertaken when they are not. Furthermore, we discuss the usefulness of dose-distribution models for estimation of expected clinical benefit and for selection of the patients' population with the highest expected benefit. Economic modelling, including the approach of real options analysis, can inform whether implementation of a technology should begin (based on available evidence) or be delayed (until further data are available), and it can indicate the best trial design and required sample size.

Lancet Oncol 2012; 13: e169–77

Maastro Clinic, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, Netherlands (J van Loon PhD)**; Department of Health Services Research, CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, Netherlands** (J Grutters PhD)**; and Centre for Clinical Practice, National Institute for Health and Clinical Excellence, London, UK** (J van Loon, F Macbeth FRCR)

Correspondence to:
Dr Judith van Loon, Maastricht Radiation Oncology (Maastro Clinic), Dr Tanslaan 12, 6229 ET Maastricht, Netherlands
judith.vanloon@maastro.nl

Introduction

More than 50% of all cancer patients receive radiotherapy as part of their anticancer treatment.[1] Over the past 10 years, planning and delivery technologies for radiotherapy have evolved rapidly, and these innovations could have contributed to improvements in clinical outcome. However, achievements of further technical refinements could be limited.[2] Technical innovations are associated inevitably with increased costs. It has been suggested that these costs should be viewed in context with either expensive systemic treatments that are reimbursed[3] or the total costs of anticancer treatment, of which radiotherapy accounts for about 5%.[4,5] But overall costs of oncology care are expected to rise,[6] and many countries now ask for evidence of the cost effectiveness of new treatments before agreeing to their general reimbursement, since resources are likely to become increasingly constrained.[6,7] Therefore, the costs associated with the introduction of technologies have to be weighed against their benefits. Ideally, any new technology should be assessed in a randomised controlled trial. Although new drugs for cancer treatment are always tested in randomised trials before their introduction into clinical practice, novel radiotherapy technologies have characteristics that make their evaluation in clinical trials more complex. Furthermore, the pricing of medical technologies is less stable than that of drugs,[8] which could make calculation of costs associated with the introduction of a new technology more difficult.

Although novel radiotherapy technologies are introduced fairly quickly into clinical practice, uncertainty can persist about both their clinical and cost effectiveness. With the increasing demand to control health-care spending, reliable evidence is needed. *The Lancet Oncology* Commission addressed challenges in delivering affordable and high-quality cancer care,[9] with a section in their report devoted specifically to assessment of radiotherapy technology. Despite its comprehensiveness, the report was criticised for scant practical solutions.[10] Here, we investigate the challenges in more detail and offer a practical way forward for evaluation of innovations in radiotherapy. Hence, we propose an algorithm for evaluation of the effectiveness of novel radiotherapy technologies on the basis of an economic modelling approach. To account for the principles underlying this algorithm, we first discuss specific difficulties in obtaining high-quality evidence about radiotherapy technologies. Second, we address potential methods for collection of such evidence and how limitations can be mitigated. After presentation of the algorithm, we discuss remaining challenges.

Difficulties obtaining high-quality evidence

First, we should distinguish between new radiotherapy techniques and technologies. A new radiotherapy technique refers to a different dose, fractionation schedule, or target volume (such as omission of elective nodal irradiation) whereas a novel radiotherapy technology refers to a new treatment modality or an important technical modification. New treatment modalities, such as intensity-modulated radiotherapy (IMRT) and particle therapy with protons and heavy ions, allow for increased conformal dose distribution around the target volume, resulting in a lower dose to surrounding healthy tissue. Novel radiotherapy technologies also include use of new imaging techniques, such as MRI and PET, in radiotherapy planning.

Novel radiotherapy techniques and technologies usually aim to increase the therapeutic ratio—ie, the balance between improved outcomes (usually survival) and toxic

effects. Raising the therapeutic ratio can be achieved either by reducing radiation dose to healthy tissues or by boosting dose to the tumour to obtain better local tumour control. Although a new radiotherapy technique (different dose or treatment volume) can be compared with the conventional technique in a randomised controlled trial, this assessment is trickier for a novel radiotherapy technology. New technologies are typically introduced uncritically, under the assumption that better dose distribution or more accurate dose delivery will ultimately yield better outcomes for patients. If new technologies cost the same as standard technologies, this process might not be a problem. However, some new technologies that have been developed for radiation planning and delivery are significantly more costly.[11–13] For both IMRT[14–16] and particle therapy,[17–22] and for several uses of radiotherapy planning based on novel imaging techniques,[23–25] evidence shows their dosimetric advantages. However, in many clinical situations, little or no evidence is available about whether and to what extent these dosimetric advantages result in clinically relevant improved outcomes for the patient.[26,27]

What evidence is needed to make decisions about the introduction of these expensive new technologies into routine clinical practice? Particular difficulties can arise with assessment of the effectiveness of new radiotherapy technologies[1,8,28] compared with new drugs. First, substantial investments have to be made in new equipment, quality assurance, and additional training of health-care professionals before clinical trials can start. Second, the technology might evolve and be modified incrementally over time, with effects on both costs and effectiveness.[29] Third, clinical outcomes associated with their use could be affected by a learning curve for health professionals[30] and by augmentation of organisational efficiency. Fourth, extended follow-up is needed to measure important outcomes such as reduction of long-term toxic effects or second (radiation-induced) malignant diseases. Fifth, obtaining commercial sponsorship is more difficult than for new drugs. Finally, ethical issues could arise in testing a theoretically superior treatment in a randomised trial—the matter of equipoise.

Because gradual modifications of a technology can increase its effectiveness or reduce its costs, study findings run the risk of being invalid by the time of publication.[31] Furthermore, a patient's overall management could change in other ways—eg, new systemic therapy or surgical procedures.

Assessment of novel radiotherapy technologies

Costs

Expenditure associated with a new technology can be divided roughly into capital (or investment) costs and operational spending.[12] Capital costs include all payments needed to make the technology available, such as outlay for construction of a new building or department and equipment overheads (linear accelerators, computers, software). Operational spending encompasses all expenses for keeping the technology running—ie, salaries, energy and utilities, maintenance, cleaning, and renewal. Although calculation of the different costs in this way might seem straightforward, several reasons show why it is not. First, assessment is difficult of the proportion of the different aspects that should specifically be attributed to the new technology. Second, to incorporate capital costs into an analysis of expenditure, a period must be set over which capital costs should be paid back. This period is difficult to estimate because devices have usually been developed recently and the time when an alternative technology will become available is typically uncertain. Furthermore, expenses can change gradually during and after implementation of a new technology. For example, investment spending for new equipment is likely to fall when the technology is applied widely. Also, with experience, efficiency will probably improve and, therefore, operational costs will fall.[30] However, in view of the evolution of technologies, some costs of treatment might rise gradually as refinements are added.[32]

One way to assess the financial outcomes of gradual process and technology changes, mainly with respect to operational spending, and factors that affect the number of patients treated per year is called activity based costing.[33,34] Breaking down the treatment activity process into small steps, such as quality assurance or inverse treatment planning, allows inclusion or exclusion of that step to be measured with respect to total costs of the process and allows the effect of any expected increase in efficiency over time to be seen. To undertake economic assessment, however, we need information not only about costs but also about the clinical effectiveness of various strategies. Results of the few economic evaluations of particle therapy[35–38] are associated with considerable uncertainty, attributable largely to uncertainties about the clinical effectiveness of this modality.

Randomised controlled trials

Randomised controlled trials are still viewed as the gold standard to assess clinical effectiveness, because random allocation of treatment minimises the effect of selection bias on the estimated treatment effect.[5] Nevertheless, whether novel radiotherapy technologies should be tested in randomised trials is debatable.[3,5,28,39–43] Apart from some subjective arguments against a randomised controlled trial (such as a strong belief in the new technology), several real limitations are important to consider (panel 1).[44] Equipoise is often cited to support the belief that randomised controlled trials in the area of technical innovation are unethical.[45,46] Although this principle might not apply to an individual clinician, who might have strong beliefs in a specific novel technology (individual equipoise), it is true for the wider clinical community (collective equipoise).[41] However, in view of the limitations, other options are still needed to obtain good data on clinical effectiveness of these technologies.

Observational studies

A prospective comparative cohort study is the type of observational study with the lowest risk of bias, and there are some important opportunities to use this trial type. Late toxic effects, such as second malignant disease or cardiac morbidity, are important for evaluation of technological innovations, and a comparative cohort study could include enough patients to detect a change in these risks. The same holds true for assessment of effectiveness in rare indications or subsets of patients, because in these groups the benefit of better dose distribution is to be expected. Furthermore, since individuals included in an observational study are more likely to be representative of the general population of patients, the external validity of the recorded treatment effect is higher than with randomised controlled trials.

Observational cohort studies should not only aim to reduce selection bias but also allow the effect of confounding factors that cannot be excluded to be estimated. To meet these requirements, an international radiotherapy register consisting of anonymised patients' data[47] could be useful. With such a database, a prospective comparative cohort study could be undertaken to compare outcomes between patients treated with a novel technology and a matched group receiving the conventional method. Furthermore, after establishing groups of people for whom the novel radiotherapy technology is effective, a database could be used to estimate the number of suitable patients and their geographical distribution.[47] This information is needed to define optimum capacity and location of centres offering the new technology. Finally, cost data can be obtained prospectively.

Although prospective comparative cohort studies have advantages over randomised controlled trials, their shortcomings are well known; methods of data collection and less strictly defined or absent inclusion criteria make findings of observational studies more susceptible to review and selection bias. When analysing outcomes such as late toxic effects or secondary malignant disease, extended follow-up is needed but is not always feasible. To allow consistent and long follow-up of patients, a reliable link between national cancer registries and survival data from population databases is needed. Another challenge is selection of an appropriate control group. Since the standard radiotherapy treatment is more likely to differ between countries than within one country, an international database is most able to allow selection of an appropriate control group. Absence of strict inclusion criteria will result in heterogeneity of treatment results across different subsets of patients. However, owing to a larger sample size, subgroup analyses to assess the treatment effect in these different categories would have greater power. Finally, unmeasured confounders might undermine the causal relation between outcome and treatment. Methods of sensitivity analysis have been developed to analyse the possible effects of these unmeasured confounders.[48] Overall, improvement of methodological standards for observational research and registries remains a challenge.[49]

***Panel 1:* Circumstances that compromise the feasibility of a randomised trial**

Rare indications
- Required sample size not reachable

Narrow inclusion criteria
- Absence of external validity

Endpoints that require data for late toxic effects or second malignant disease
- Unacceptable length of follow-up period
- Large sample size needed

Limited funding
- Insufficient resources to undertake a randomised trial

Strong belief in effectiveness of the novel technique
- Lack of willingness to participate in a randomised trial

Recently, international prospective databases have been set up—eg, for rectal and cervical carcinoma. In both databases, characteristics of the tumour, patient, and their treatment are gathered prospectively. The rectal cancer database,[50] which combines population-based databases from four institutes across three different countries, has been set up to predict the outcome of chemoradiotherapy on the basis of patient's and image characteristics. The EMBRACE study in cervical cancer (NCT00920920) currently includes 300 patients from 18 centres across Europe, with the aim of correlating image-based dose-distribution variables with outcome. Although these databases are restricted to one cancer site and, until now, have only short follow-up, they provide evidence that this approach is feasible.

Models

When evidence from clinical trials on the effectiveness of novel technologies is not available, models can be used to predict their potential clinical benefit because of better dose distribution or increased biological effectiveness. Modelling can give valuable insights into which technologies are worth further investigation, and for which indications.

Dose–response models

Planning studies are used extensively to quantify differences in dose distribution between treatment techniques.[18,51,52] They use computer-based algorithms to predict dose received by different organs and the tumour. Nevertheless, the extent to which improvements in dose distribution affect clinically relevant outcomes is uncertain. Quantification of this effect through normal tissue complication probability and tumour control probability models is still uncertain.[53–55] This doubt is complicated further when the new technology entails possible

differences in relative biological effect, such as with carbon ions. In some situations, current state-of-the-art radiotherapy techniques are not feasible because the tumour is too close to the organs at risk—eg, with skull base tumours. In these circumstances, superiority of a novel technology solely on the basis of better dose conformality around the tumour should be judged sufficient evidence to apply the novel treatment. In all other cases, superiority on the basis of dose–distribution models cannot be deemed a substitute for prospective studies of adequate size. For these indications, dose–distribution models are mainly useful to identify tumour types and locations that are most likely to benefit from the new technology and to provide an estimate of the predicted size of this benefit. Data from these models can provide helpful information about the design of future clinical trials, such as for calculation of sample size or definition of the research population.[27]

Economic modelling

Economic modelling can help decide whether to implement a novel radiotherapy strategy on the basis of evidence that is currently available from different sources. Results are expressed commonly by the incremental cost effectiveness ratio, calculating incremental costs per quality-adjusted life-year (QALY) gained with the novel strategy. With QALYs, both mortality and morbidity are included, by correcting the remaining life-years for their health-related quality. Obviously, the more uncertain the inputs for the model are, the more tentative the results will be. We can assess this uncertainty by doing a sensitivity analysis that looks at the effect of changes in different inputs (eg, a reduction in costs) on the incremental cost effectiveness ratio. Although this analysis is an accurate way to incorporate uncertainty, a choice still has to be made that inevitably carries the risk of making a wrong decision. Patients might then receive a suboptimum treatment (opportunity costs) or money could be spent on an ineffective new treatment.

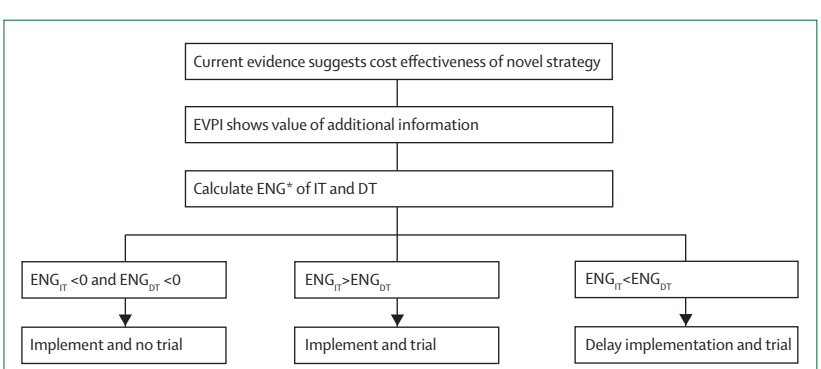

Figure 1: **Real options analysis**
ENG=expected net gain. EVPI=expected value of perfect information. IT=implement and trial. DT=delay implementation and trial. *Calculate ENG as: (total expected benefits)–(total expected costs). An overview of expected costs and benefits per strategy is provided in the table.

Additional research would reduce uncertainty surrounding input variables and, thus, the chance of making a wrong decision. The value of extra information needs to be balanced against the costs of acquiring additional knowledge. Information on whether additional research is worth the extra costs can be obtained by Bayesian techniques analysing the value of additional information.[37,56] The expected value of perfect information (EVPI) provides a measure of the worth (expressed in monetary terms) of acquiring perfect information, and the expected value of sample information (EVSI) assesses the worth of acquiring information through a trial of a known size.[57] A drawback of these techniques is that they assume implicitly that a technology is available for the trial. If a cost-effective technology (based on economic modelling) is implemented and subsequent evidence shows that it is not cost effective and a wrong decision was made, costs are associated with reversal of that decision.

Particularly with new radiotherapy technologies, for which investment costs are high, the option to delay the decision to implement to a later time—when more information on clinical and cost effectiveness is available—would be of great value. However, a hold-up in implementation implies that patients are withheld a potentially cost-effective treatment. Real options analysis allows us to incorporate the option to delay. This approach originates from the area of finance and has been introduced to inform further research in health care.[57–59] Palmer and colleagues[58] say uncertainty, irreversibility, and the ability to defer outlay are characteristics of health-care investments that make real options analysis especially useful. Novel radiotherapy technologies clearly have these three features: substantial uncertainty exists about expected clinical benefit, and reversal costs are high not only due to the cost of investment but also because the product invested in would not yield much money when resold.

Two trade-offs have to be made before the best strategy can be ascertained. First, we must decide whether to undertake additional research on the basis of the expected value of additional information. Second, delayed implementation needs to be analysed, by comparing expected costs of reversal with expected opportunity costs of giving patients a suboptimum treatment during the period of the trial (figure 1). The table shows expected costs and benefits for the different strategies. Apart from providing information on these trade-offs, real options analysis helps define the best trial design, including sample size, endpoints, and length of follow-up.[57] One way to delay the decision to implement is the so-called coverage with evidence development approach, which is used in UK National Institute for Health and Clinical Excellence (NICE) health technology appraisals.[60,61] With this approach, a technology is implemented temporarily and all patients are monitored to obtain further information, after which the final decision is made. This strategy is used for assessment of drugs, for which the decision is

reversible without substantial expense. When reversal costs are high, however, treatment of all patients with the new technology for a limited time is not feasible. In these cases, real options analysis should be used to inform the trial design associated with the option to delay. Dose–response and economic models can eventually be integrated with real options analysis, as has been done with proton therapy for prostate cancer.[38]

Modelling approaches have some important drawbacks. First, the decision model is built to reflect reality as closely as possible but can never be perfect. Second, models are especially useful when evidence is either absent or incomplete. However, assumptions have to be made and, hence, the output of models is always uncertain. Therefore, modelling is not a substitute for high-quality evidence but rather a supplement. Finally, results are only valid for the specific region or country for which the analysis was set up: both costs and expected benefits associated with different strategies can differ substantially between countries. In economic modelling, selection of the appropriate perspective for the analysis is important, which will differ in various jurisdictions depending on the method of health-care funding. As a general rule, a broad perspective should be chosen that indicates the best treatment for society as a whole, rather than a narrower hospital-based or individual-based perspective. A model does not need to be rebuilt for every perspective: it can be run again with adapted inputs for different jurisdictions.[62]

Algorithm for clinical trial designs

Study designs

Randomised controlled trials should be undertaken whenever possible. When they are not feasible however (panel 1), prospective comparative cohort studies with the establishment of national or international therapy registers, in which data are gathered prospectively and anonymously, are preferred. Panel 2 outlines guidelines for collection of effectiveness data through a prospective comparative cohort study. Collection and analysis of data should be similar for all participating centres and, therefore, be organised and monitored centrally.

Assessment of the difference between treatments should focus on components related to the novel treatment technology and not to other factors in the treatment process.[63] In other words, state-of-the-art conventional radiotherapy should be compared with state-of-the-art radiotherapy including the novel technology. This distinction is important: for example, particle therapy is delivered (so far) mainly in centres primarily built for research sometimes using suboptimum quality assurance and fractionation schedules compared with centres delivering state-of-the-art three-dimensional (3D) conformal photon therapy (the current conventional radiotherapy with which the novel therapy should be compared).[47] Also, ideally, the geographical areas from which patients are enrolled should be broadly similar, since both known and unknown environmental and lifestyle factors and ethnic mix could bias outcome.[64] However, in practice, comparability might not always be possible because institutions offering advanced new treatments are generally tertiary referral centres.[27] Therefore, prospective collection of patients' characteristics and potential predictive factors at least allows for multivariate analysis to establish the effect of those factors and correct for heterogeneity between studies.[65]

	Costs	Benefits
Implement and no trial	None	None
Implement and trial	Reversal costs and trial costs	Reduced uncertainty after trial
Delay implementation and trial*	Opportunity costs† and trial costs	Reduced uncertainty after trial

*When delay implementation and trial is the preferred option, the novel strategy should be available during this period for research purposes. If the novel strategy is not yet available, investments should be directed at construction of a specific research centre using the technique. In this case, reversal costs of building this centre should be taken into account but will be far less than those of implementing the strategy for daily clinical practice. †Costs associated with patients in the trial undergoing a suboptimum treatment for the duration of the trial.

Table: **Costs and benefits of strategies in real options analysis**

Panel 2: **Guidelines for prospective observational cohort studies on novel radiotherapy techniques**

Comparison of two state-of-the-art treatment techniques

- Novel technique must be available in (research) setting that adheres to clinical standards of state-of-the-art conventional treatment

Comparable techniques between centres

- Define criteria for:
  - Planning technique
  - Quality control
  - Amount of beams
  - Total dose and fraction size

Comparable patient populations

- Include patients from similar geographical areas
- Collect baseline characteristics:
  - Age
  - WHO performance score
  - Sex
  - Comorbidity
  - Socioeconomic status
  - Quality of life
  - Stage
  - Histological features
  - Tumour location

Analysis of influence of potential confounding factors

- Collect treatment characteristics:
  - EQD_2 (biologically equivalent dose in 2 Gy fractions)
  - Period of treatment
  - Other types of treatment
- Perform multivariate analysis on potential predictors of outcome:
  - Baseline and treatment characteristics

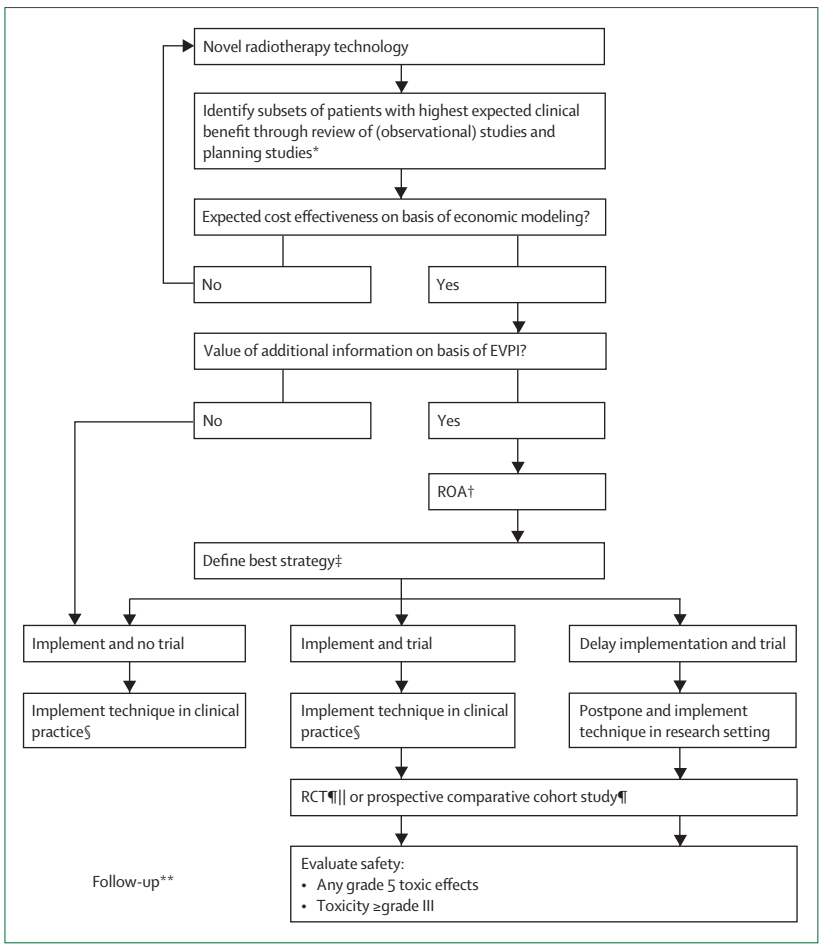

Figure 2: **Algorithm for evaluation of novel radiotherapy technologies**
CTCAE=common terminology criteria for adverse events. EQ-5D=EuroQol 5 dimensions. EVPI=expected value of perfect information. PERCIST=PET response criteria for solid tumours. QLQ-C30=EORTC quality of life questionnaire C30. RCT=randomised controlled trial. RECIST=response evaluation criteria in solid tumours. ROA=real options analysis. *On the basis of panel 1. Endpoints are overall survival or quality adjusted survival. †Defined by best trial design (RCT if possible) and perspective. ‡On the basis of figure 1. §Minimum criteria defined on planning technique, dose constraints, fractionation, and quality control. ¶Defined on the basis of ROA: sample size and follow-up period. ||Stratification by age, WHO performance score, location, stage, and centre. **Gather data for radiotherapy variables, toxic effects (CTCAE version 4.0), quality of life (EQ-5D and QLQ-C30), progression (RECIST and PERCIST), and costs.

Modelling

Having established guidance for the type of trial that should be undertaken under different conditions, preliminary data are needed to define other trial characteristics, such as study population and sample size. Planning studies in combination with models for normal tissue complication probability and tumour control probability can help to identify populations that are most likely to benefit and provide an estimate of the predicted size of this gain. Another approach that can complement dose-distribution models is meta-analysis of clinical data from small observational studies, although this approach has drawbacks. For example, bias will arise because of differences in patients' and treatment characteristics, and the resulting heterogeneity between studies can only be corrected for when individual studies are large enough.[55] Furthermore, in observational studies, different confounding variables are typically reported inconsistently.[66–68] Similarly, inconsistency and incompleteness will apply to reporting of endpoints important for evaluation of novel radiotherapy technologies, such as late effects, second malignant diseases, and quality of life. Even so, without randomised controlled trials, meta-analyses of data from observational studies provide a way to obtain evidence of expected clinical benefit.

Overall, meta-analyses of observational studies in combination with data from dose-distribution models can give an idea of expected clinical benefit and the subgroups of patients most likely to benefit. These estimates, including uncertainty surrounding them, can then be used in an economic model. The economic modelling approach, including real options analysis, provides further information on whether to delay implementation of novel technology and whether to undertake additional research, and on the best sample size and endpoints.

Algorithm

Figure 2 shows graphically the proposed algorithm for assessment of novel radiotherapy technologies, based on the steps described above. Subsets of patients with the highest expected clinical benefit should be identified through dose-distribution models and, when (observational) studies are available, a meta-analysis thereof. An estimate of expected benefit can also be obtained from these sources. Subsequently, cost effectiveness modelling (including real options analysis) informs the decision whether to implement and trial, delay and trial, or implement the technique without further research. On the basis of criteria in panel 1, in combination with the results of real options analysis, the best trial design can be ascertained. Selection criteria for the trial can be derived from characteristics of patients' subgroups with the highest expected clinical benefit, and the optimum sample size and endpoints can be established by real options analysis.

Trial endpoints should indicate the cost effectiveness of a strategy and be expressed (preferably) in costs per QALY gained. Prospective data collection for costs and quality of life is therefore needed. We recommend use of the validated questionnaires EQ-5D (EuroQol-5 dimensions)[69] and QLQ-C30 (the European Organisation for Research and Treatment of Cancer quality of life questionnaire C30), to which a questionnaire specific to the type of cancer can be added. The threshold of the incremental cost effectiveness ratio that should be used as a cut-off for cost effectiveness will vary from country to country.[70] Inclusion of radiotherapy variables, such as dose–volume histograms, in the prospective database allows accuracy of normal tissue complication probability and tumour control probability models to be increased, which will reduce uncertainty surrounding the estimate of the expected gain of novel treatment technologies in the future.[71]

Importantly, the decision to implement a new treatment technology on the basis of economic modelling has implications for acquisition of further evidence for clinical efficacy. Once a new technology has been approved and reimbursed, manufacturers and doctors are unlikely to do further research. When results of a model show that implement and trial is the preferred option, recommendations for further research should be described explicitly and incorporated in the reimbursement decision as a binding statement. Until now, reimbursement agencies have little, if any, authority to ensure this research is done.[72,73] Furthermore, one may assume that new information only becomes available from within a trial. In reality, other options exist, such as delay and no trial or delay and make a side payment to, or enlarge, a current trial that is already investigating the technology.

Remaining challenges

Even if an international prospective database were set up, some drawbacks are unavoidable. Although required resources will be considerably fewer than for randomised controlled trials, funding is still needed. Financial contributions from manufacturers of radiotherapy technology might not be as great as for pharmaceutical companies, so funding is likely to be a real issue.[1] Until now, focus has been mainly on funding of randomised controlled trials, thus manufacturers, research bodies, and governments, should be made aware of use of observational studies through prospective (international) databases. As stated in *The Lancet Oncology* Commission Report,[9] the issues in setting up these databases are ethical, political, and administrative rather than technical. Our focus on use of observational research and registries is in line with recent developments in comparative effectiveness research.[49] In the USA, comparative effectiveness research has been taken up by the National Institutes of Health as a means to create evidence that is useful for making health policy decisions. A main coordinating role in international collaboration could be adopted by the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO). An initiative has already been set up within ESTRO, the Health Economics in Radiation Oncology (HERO) project, with the aim of developing a basis for health economic evaluation of radiotherapy at a European level.

In view of incremental changes in radiotherapy, clinical results obtained and costs associated with any novel technology will change continuously. No agreement has been reached on how to incorporate these gradual changes. The clinical benefit of every small step will never be testable in an adequately powered trial. A method should be developed to detect the point at which to recommend a prospective study of a fast-changing technology, to assess the benefit of a series of small changes. Strategies have been described for how to detect such an important point in bibliometric studies on citation and publication trends.[31,74]

Search strategy and selection criteria

Our report is not intended to provide a complete and comprehensive literature review. However, we undertook a search of PubMed to ensure that all published work relevant to the issue was covered, with the terms "evidence based medicine", "cost-effectiveness", "health economic evaluation", "health technology evaluation", and "real options analysis", in combination with "radiotherapy", "radiation", "particle therapy", or "proton therapy". We selected papers for their possible relevance to evaluation of the clinical worth and cost-effectiveness of radiation technologies and therapy. Moreover, we searched reference lists of all relevant articles to identify further studies. Furthermore, reports and ongoing studies on this subject that were known by the authors were included. Only reports published in English and available online between January, 1995, and Oct 5, 2011, were included. We had no restriction on type of study.

When a technology is implemented on the basis of its cost effectiveness, the risk exists that it will also be applied to tumour sites or patients for whom clinical benefit has not been proven. Because this broadening of indications is likely to be less cost effective, indications should be monitored carefully.

Finally, arguments other than cost effectiveness alone exist for investment in novel technologies. Commercial competition, research incentives, or education are all important and, thus, investment in specific research centres with state-of-the-art physical and clinical facilities is strongly recommended.

Contributors

The literature search was done by JvL, JG, and FM. Study design and figures were developed by JvL, JG, and FM. Data collection and analysis was done by JvL. Data interpretation and analysis was performed by JvL, JG, and FM.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

JvL did most of this work during a 3-month visit to the National Institute for Health and Clinical Excellence, London, UK, funded by the Dutch Cancer Society and the European Society for Radiotherapy and Oncology (ESTRO).

References

1 Mattsson S, Brahme A, Carlsson J, et al. Swedish Cancer Society radiation therapy research investigation. *Acta Oncol* 2002; **41:** 596–603.
2 Bentzen SM. High-tech in radiation oncology: should there be a ceiling? *Int J Radiat Oncol Biol Phys* 2004; **58:** 320–30.
3 Goitein M, Cox JD. Should randomized clinical trials be required for proton radiotherapy? *J Clin Oncol* 2008; **26:** 175–76.
4 Lievens Y, Van den Bogaert W. Proton beam therapy: too expensive to become true? *Radiother Oncol* 2005; **75:** 131–33.
5 Bentzen SM. Randomized controlled trials in health technology assessment: overkill or overdue? *Radiother Oncol* 2008; **86:** 142–47.
6 Meropol NJ, Schrag D, Smith TJ, et al. American Society of Clinical Oncology guidance statement: the cost of cancer care. *J Clin Oncol* 2009; **27:** 3868–74.
7 Drummond MF, Mason AR. European perspective on the costs and cost-effectiveness of cancer therapies. *J Clin Oncol* 2007; **25:** 191–95.

8 National Institute for Health and Clinical Excellence. Medical technologies evaluation programme: process guide. April, 2011. http://www.nice.org.uk/media/4E0/F7/MedicalTechnologiesEvaluationProgrammeProcessGuide.pdf (accessed Jan 27, 2012).

9 Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011; **12:** 933–80.

10 Rawlins MD, Chalkidou K. The opportunity cost of cancer care: a statement from NICE. *Lancet Oncol* 2011; **12:** 931–32.

11 Konski A, Watkins-Bruner D, Feigenberg S, et al. Using decision analysis to determine the cost-effectiveness of intensity-modulated radiation therapy in the treatment of intermediate risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2006; **66:** 408–15.

12 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.

13 Goitein M, Jermann M. The relative costs of proton and X-ray radiation therapy. *Clin Oncol (R Coll Radiol)* 2003; **15:** S37–50.

14 Huang D, Xia P, Akazawa P, et al. Comparison of treatment plans using intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for paranasal sinus carcinoma. *Int J Radiat Oncol Biol Phys* 2003; **56:** 158–68.

15 Xia P, Fu KK, Wong GW, et al. Comparison of treatment plans involving intensity-modulated radiotherapy for nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2000; **48:** 329–37.

16 De Meerleer GO, Vakaet LA, De Gersem WR, et al. Radiotherapy of prostate cancer with or without intensity modulated beams: a planning comparison. *Int J Radiat Oncol Biol Phys* 2000; **47:** 639–48.

17 Baumert BG, Lomax AJ, Miltchev V, et al. A comparison of dose distributions of proton and photon beams in stereotactic conformal radiotherapy of brain lesions. *Int J Radiat Oncol Biol Phys* 2001; **49:** 1439–49.

18 Cozzi L, Fogliata A, Lomax A, et al. A treatment planning comparison of 3D conformal therapy, intensity modulated photon therapy and proton therapy for treatment of advanced head and neck tumours. *Radiother Oncol* 2001; **61:** 287–97.

19 Fogliata A, Bolsi A, Cozzi L. Critical appraisal of treatment techniques based on conventional photon beams, intensity modulated photon beams and proton beams for therapy of intact breast. *Radiother Oncol* 2002; **62:** 137–45.

20 Isacsson U, Lennernas B, Grusell E, et al. Comparative treatment planning between proton and x-ray therapy in esophageal cancer. *Int J Radiat Oncol Biol Phys* 1998; **41:** 441–50.

21 Lee CH, Tait D, Nahum AE, et al. Comparison of proton therapy and conformal X-ray therapy in non-small cell lung cancer (NSCLC). *Br J Radiol* 1999; **72:** 1078–84.

22 St Clair WH, Adams JA, Bues M, et al. Advantage of protons compared to conventional X-ray or IMRT in the treatment of a pediatric patient with medulloblastoma. *Int J Radiat Oncol Biol Phys* 2004; **58:** 727–34.

23 De Ruysscher D, Wanders S, Minken A, et al. Effects of radiotherapy planning with a dedicated combined PET-CT-simulator of patients with non-small cell lung cancer on dose limiting normal tissues and radiation dose-escalation: a planning study. *Radiother Oncol* 2005; **77:** 5–10.

24 van Loon J, Offermann C, Bosmans G, et al. 18FDG-PET based radiation planning of mediastinal lymph nodes in limited disease small cell lung cancer changes radiotherapy fields: a planning study. *Radiother Oncol* 2008; **87:** 49–54.

25 Ciernik IF, Dizendorf E, Baumert BG, et al. Radiation treatment planning with an integrated positron emission and computer tomography (PET/CT): a feasibility study. *Int J Radiat Oncol Biol Phys* 2003; **57:** 853–63.

26 Veldeman L, Madani I, Hulstaert F, De Meerleer G, Mareel M, De Neve W. Evidence behind use of intensity-modulated radiotherapy: a systematic review of comparative clinical studies. *Lancet Oncol* 2008; **9:** 367–75.

27 Brada M, Pijls-Johannesma M, De Ruysscher D. Current clinical evidence for proton therapy. *Cancer J* 2009; **15:** 319–24.

28 Glimelius B, Montelius A. Proton beam therapy: do we need the randomised trials and can we do them? *Radiother Oncol* 2007; **83:** 105–09.

29 Zietman A, Goitein M, Tepper JE. Technology evolution: is it survival of the fittest? *J Clin Oncol* 2010; **28:** 4275–79.

30 Bonastre J, Noel E, Chevalier J, et al. Implications of learning effects for hospital costs of new health technologies: the case of intensity modulated radiation therapy. *Int J Technol Assess Health Care* 2007; **23:** 248–54.

31 Wild C, Langer T. Emerging health technologies: informing and supporting health policy early. *Health Policy* 2008; **87:** 160–71.

32 Ploquin NP, Dunscombe PB. The cost of radiation therapy. *Radiother Oncol* 2008; **86:** 217–23.

33 Dunscombe P, Roberts G, Walker J. The cost of radiotherapy as a function of facility size and hours of operation. *Br J Radiol* 1999; **72:** 598–603.

34 Lievens Y, van den Bogaert W, Kesteloot K. Activity-based costing: a practical model for cost calculation in radiotherapy. *Int J Radiat Oncol Biol Phys* 2003; **57:** 522–35.

35 Mobaraki A, Ohno T, Yamada S, et al. Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer. *Cancer Sci* 2010; **101:** 1834–39.

36 Lundkvist J, Ekman M, Ericsson SR, et al. Proton therapy of cancer: potential clinical advantages and cost-effectiveness. *Acta Oncol* 2005; **44:** 850–61.

37 Grutters JP, Pijls-Johannesma M, Ruysscher DD, et al. The cost-effectiveness of particle therapy in non-small cell lung cancer: exploring decision uncertainty and areas for future research. *Cancer Treat Rev* 2010; **36:** 468–76.

38 Konski A, Speier W, Hanlon A, et al. Is proton beam therapy cost effective in the treatment of adenocarcinoma of the prostate? *J Clin Oncol* 2007; **25:** 3603–08.

39 Glatstein E, Glick J, Kaiser L, et al. Should randomized clinical trials be required for proton radiotherapy? An alternative view. *J Clin Oncol* 2008; **26:** 2438–39.

40 Goitein M. Trials and tribulations in charged particle radiotherapy. *Radiother Oncol* 2010; **95:** 23–31.

41 Macbeth FR, Williams MV. Proton therapy should be tested in randomized trials. *J Clin Oncol* 2008; **26:** 2590–91.

42 Suit H, Kooy H, Trofimov A, et al. Should positive phase III clinical trial data be required before proton beam therapy is more widely adopted? No. *Radiother Oncol* 2008; **86:** 148–53.

43 Tepper JE. Protons and parachutes. *J Clin Oncol* 2008; **26:** 2436–37.

44 Rawlins M. *De testimonio*: on the evidence for decisions about the use of therapeutic interventions. *Lancet* 2008; **372:** 2152–61.

45 Meropol NJ. A renewed call for equipoise. *J Clin Oncol* 2007; **25:** 3392–94.

46 Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987; **317:** 141–45.

47 Lodge M, Pijls-Johannesma M, Stirk L, et al. A systematic literature review of the clinical and cost-effectiveness of hadron therapy in cancer. *Radiother Oncol* 2007; **83:** 110–22.

48 VanderWeele TJ, Mukherjee B, Chen J. Sensitivity analysis for interactions under unmeasured confounding. *Stat Med* 2011; published online Oct 4, 2011. DOI:10.1002/sim.4354.

49 Helfand M, Tunis S, Whitlock EP, et al. A CTSA agenda to advance methods for comparative effectiveness research. *Clin Transl Sci* 2011; **4:** 188–98.

50 van Stiphout RG, Lammering G, Buijsen J, et al. Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging. *Radiother Oncol* 2011; **98:** 126–33.

51 Roelofs E, Persoon L, Qamhiyeh S, et al. Design of and technical challenges involved in a framework for multicentric radiotherapy treatment planning studies. *Radiother Oncol* 2010; **97:** 567–71.

52 Zurlo A, Lomax A, Hoess A, et al. The role of proton therapy in the treatment of large irradiation volumes: a comparative planning study of pancreatic and biliary tumors. *Int J Radiat Oncol Biol Phys* 2000; **48:** 277–88.

53 Tubiana M, Eschwege F. Conformal radiotherapy and intensity-modulated radiotherapy: clinical data. *Acta Oncol* 2000; **39:** 555–67.

54 Bentzen SM, Constine LS, Deasy JO, et al. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. *Int J Radiat Oncol Biol Phys* 2010; **76:** S3–9.

55 Ramaekers BL, Pijls-Johannesma M, Joore MA, et al. Systematic review and meta-analysis of radiotherapy in various head and neck cancers: comparing photons, carbon-ions and protons. *Cancer Treat Rev* 2011; **37:** 185–201.

56 Claxton K, Posnett J. An economic approach to clinical trial design and research priority-setting. *Health Econ* 1996; **5:** 513–24.

57 Eckermann S, Willan AR. Expected value of information and decision making in HTA. *Health Econ* 2007; **16:** 195–209.

58 Palmer S, Smith PC. Incorporating option values into the economic evaluation of health care technologies. *J Health Econ* 2000; **19:** 755–66.

59 Grutters JP, Abrams KR, De Ruysscher D, et al. When to wait for more evidence? Real options analysis in proton therapy. *Oncologist* 2011; **16:** 1752–61.

60 Briggs A, Ritchie K, Fenwick E, et al. Access with evidence development in the UK: past experience, current initiatives and future potential. *Pharmacoeconomics* 2010; **28:** 163–70.

61 Chalkidou K, Lord J, Fischer A, et al. Evidence-based decision making: when should we wait for more information? *Health Aff (Millwood)* 2008; **27:** 1642–53.

62 Welte R, Feenstra T, Jager H, et al. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoeconomics* 2004; **22:** 857–76.

63 Black N. Why we need observational studies to evaluate the effectiveness of health care. *BMJ* 1996; **312:** 1215–18.

64 Erridge SC, Murray B, Williams L, et al. Improved survival from lung cancer in British Columbia compared to Scotland: are different treatment rates the whole story? *Lung Cancer* 2009; **64:** 358–66.

65 Macbeth F. Measuring the outcomes of lung cancer treatment. *J Thorac Oncol* 2008; **3:** 455–56.

66 Blettner M, Sauerbrei W, Schlehofer B, et al. Traditional reviews, meta-analyses and pooled analyses in epidemiology. *Int J Epidemiol* 1999; **28:** 1–9.

67 Stroup DF, Berlin JA, Morton SC, et al, for the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000; **283:** 2008–12.

68 Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010; **95:** 32–40.

69 The EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. *Health Policy* 1990; **16:** 199–208.

70 Ubel PA, Hirth RA, Chernew ME, et al. What is the price of life and why doesn't it increase at the rate of inflation? *Arch Intern Med* 2003; **163:** 1637–41.

71 Deasy JO, Bentzen SM, Jackson A, et al. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. *Int J Radiat Oncol Biol Phys* 2010; **76:** S151–54.

72 Sculpher M, Claxton K. Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty: when is there sufficient evidence? *Value Health* 2005; **8:** 433–46.

73 Griffin SC, Claxton KP, Palmer SJ, et al. Dangerous omissions: the consequences of ignoring decision uncertainty. *Health Econ* 2011; **20:** 212–24.

74 Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L. When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies. *Health Technol Assess* 1997; **1:** 1–149.