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**EDITORIAL**

# The future of IGRT – Cost Benefit Analysis

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The aim of image guided radiotherapy (IGRT) is to improve tumour coverage and spare normal tissues [1–23]. Higher rates of local control and lower toxicity, without doubt, are of benefit for the patient. Therefore cost-benefit analysis of IGRT should clearly be in favor of IGRT compared to standard radiation treatment. However, very little direct high level scientific evidence has been so far provided by radiation oncologists that IGRT is superior to more conventional radiotherapy techniques. This makes it difficult if not impossible to assess the cost-benefit of this treatment according to currently agreed principles of evidence based medicine (EBM). Possible ways out of this dilemma are either stringent adherence of the radiotherapy community to EBM principles when new technologies are assessed or development of scientific sound alternative methodologies for clinical technology assessment.

Economic analysis of health care interventions compares costs with outcome [24]. Both, costs and outcome can be further differentiated (Table I). It is obvious that implementation of IGRT increases the costs for the department and the hospital. The most important cost factors can be derived from the workflow of implementing and running IGRT in clinical practice [20, 23]. IGRT needs investment into specialized equipment such as in-room imaging facilities. However it usually also needs additional human resources to utilize this equipment, e.g. for performing and analyzing a cone beam CT before each or selected treatment session(s) and for deciding on adequate interventions, e.g. on adapting the isocenter or even the target volume. Reduced throughput of patients per treatment machine because of these complex and possibly time consuming tasks may further increase the need for technical and human resources. In the department of the authors, for example, the implementation of IGRT for patients with prostate carcinoma increased the in-room time per fraction on average by 32% for use of an orthogonal x-ray system and by 84% when an in-room CT on rails was used compared to conventional patient set-up by wall-lasers (Alheit, Csere et al., unpublished data). Many other factors may add to the costs for the institution, including specialized IGRT training, more demanding quality assurance, consumables and the need to increase data storage capacities.

More difficult to judge than the costs of a novel intervention for the specific provider is whether the overall medical costs, and thereby the costs for health care insurances or society, increase by IGRT. These costs also include for example additional medications or hospitalization for treatment related toxicities or additional interventions for recurrent tumours. As these interventions are not necessarily performed by the same department or hospital providing the intervention of interest, the costs related to these secondary interventions are often not included in cost-benefit analyses. To obtain solid data for these costs detailed longitudinal studies documenting prospectively all costs before,

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Table I. Economic analysis of heath care interventions (summarized from [23]).

| Cost | Outcome |
|---|---|
| Direct medical costs | Economic heath care analysis perspective |
| Direct non-health care costs | Societal perspective |
| Changes in use of informal caregiver time | Patient perspective |
| Patient time costs | Payer perspective |

during and after specific interventions for unbiased and large enough cohorts of patients are necessary.

The overall costs have to be judged against the benefit of the intervention, i.e. against outcome parameters such as survival, disease free survival, reduction of toxicity etc. Over the last two decades, wide consensus has been reached on categorizing medical evidence by levels (Table II) ranging from expert opinion (lowest level of evidence) to meta-analysis of randomized clinical trials (highest levels of evidence). To judge whether a new treatment is superior to the conventional intervention, health care insurers and policy makers but equally so medical professionals usually strive for the highest level of evidence, i.e. for evidence coming from large randomized trials. In the context of cost benefit analysis often an arbitrary cut-off of $50 000 per life year gained is chosen to discriminate cost-effective from non–cost-effective interventions. Such analysis can be further refined, and for example integrate quality of life (quality adjusted life years, QUALYs). It should be noted, however, that few investigations are available that integrate secondary costs (see above) into such cost-benefit analysis. While this is true for all fields of medicine, it is of particular concern for the field of radiation oncology as late normal tissue reactions may importantly impact the quality of life of patients and may be produce additional costs for further (often long-term) interventions. If, at the same rate of local tumour control, the incidence and severity of late normal tissue reactions can be decreased by advanced radiation technology, and if this is not considered by overall prospective cost-benefit analysis, a clear bias against the innovation may result. Consideration of early normal tissue reactions as a surrogate will not overcome this problem as it is well documented from radiobiological investigations and clinical studies that early and late normal tissue reactions may dissociate [25]. In addition the costs of interventions of early normal tissue reactions are not identical to the costs for late normal tissue reactions. It is important to note that economical modeling, under appropriate restrictions particularly with regard to patient selection bias, can also be applied in situations where randomized data are not available [24, 26]. Again, data sets need to include detailed long term information on secondary costs to prevent biased conclusions.

Table II. Levels of evidence.

| Level | Description |
|---|---|
| Ia | Meta-analysis of randomized trials |
| Ib | Large randomized trials |
| II | Case control or cohort studies |
| III | Case report, case series |
| IV | Expert opinion |

Beside of (currently non-available) randomized clinical outcome studies and thorough prospective cost-benefit analysis of IGRT versus current state of the art conformal radiotherapy techniques, radiobiological reasoning might be an adequate starting point for assessing and modeling cost-benefit of IGRT. The aim of curative radiotherapy is to kill all cancer stem cells, i.e. those cells which, when surviving radiation, can form a recurrence [27]. If imaging helps to find and hit the cancer stem cells, it will be of benefit for the patient. This actually has been the basis for surgical as well as radiotherapeutic interventions for more than hundred years, and it clearly is ethically not acceptable to address this question in a randomized trial. Scientific evaluation is possible in careful retrospective studies which independently compare tumour coverage with tumour control [20,28]. Radiation-dose response models for local tumour control [25,27], when combined with detailed data on radiation tumour coverage during the course of treatment, offer a scientific basis for estimating the potential magnitude of the impact of novel technological intervention on tumour control. The argument of tumour coverage alone does not suffice to corroborate the need for IGRT in its modern meaning, i.e. with in-room imaging to overcome geographical miss caused by inter- and interfractional inaccuracies of patient positioning and tumour movement. This can more easily be achieved by applying more extensive margins. However, thorough assessment of outcome in radiotherapy always means to assess both, local tumour control as well as normal tissue toxicity [29]. The endpoint of relevance in this context is uncomplicated local tumour control, i.e. complete inactivation of all cancer stem cells without serious normal tissue damage. This endpoint allows us to judge whether a novel intervention increases the therapeutic ratio compared with the current standard treatment. There is unequivocal evidence from a host of preclinical and clinical studies that the risk of radiation damage in normal tissues depends not only on dose, fractionation, genetic sensitivity, etc. but also importantly on dose-volume parameters in

normal tissues [25]. Early and late normal tissue damage increases with the volume of normal tissue irradiated. Therefore smaller margins around the gross tumour volume will reduce the incidence and severity of normal tissue damage. IGRT techniques have been shown to have the potential to reduce margins compared to current conformal treatment techniques [21,23] and, from a radiobiological point of view, will be able to reduce radiation induced morbidity. This, however, needs to be clinically demonstrated. It is the opinion of the authors that randomized trials have contributed substantially to progress in the field of radiation oncology and should be performed whenever appropriate. However at the same time we feel that randomized trials can not be simplistic considered as the one and only "gold standard" for all situations, because, for a variety of reasons, they are not always applicable or not advantageous for assessment of radiation techniques and technologies:

1. Ethical consideration may hinder radiation oncologists as well as ethics committees to accept randomization, because the arms may be judged not to be fair.
2. Patients, after informed consent, may reject randomization.
3. Patient referral to specific centers may be based on the provision of specialized radiation techniques.
4. Patients and their doctors wish treatment with the most "modern" technology.
5. Anatomy, as well as individual tumour location, -extension and movement in the individual patient are highly important determinants for the dose-volume parameters. Randomization procedures are usually used to evenly distribute undetected heterogeneity of important patient-related factors over the treatment arms. This will reduce potential impact of e.g. genetic radiosensitivity and co-morbidity on normal tissue reactions and of differences in tumour biology on the chance for local tumour control. However, the dose distribution in normal tissues and tumours is not an unknown confounder, and randomization will not help to reduce the vast impact which the radiation-dose distribution will have on the results. State of the art radiobiological modeling of high quality location- and dose-correlated outcome data needs to be applied for detailed evaluation, and this is true for randomized as well as non-randomized data sets. In case of non-randomized studies more patient patient-related parameters that may affect the results need to be documented. Their consideration in the models may compensate at least in parts the potential disadvantage of heterogenous distribution of other confounders.
6. Based on experiences and preferences but also on the specific technologies available, dose distributions generated in different centers may differ substantially even for the same patient. This decreases substantially the scientific power of multi-institutional trials on technology assessment in radiotherapy. Centralized planning may theoretically reduce this problem, but for many, including ethical and legal reasons, this has not been established as a standard for clinical trials.
7. Technological developments are fast and depend at best marginally on the results of clinical trials. Results of randomized trials, which often take much longer to be completed than initially expected, may already be completely outdated and irrelevant when available.

At the same time several current developments are expected to put radiation oncologists and medical physicists under considerable pressure to further improve the conformality of their treatment.

1. Because of demographic developments the age of patients receiving radiotherapy is constantly increasing. Although not well investigated (i.e. including studies on functional and outcome parameters) it is likely that, because of co-morbidity, the risk of normal tissue damage in this patient population may be increased.
2. Multidisciplinary approaches are steadily increasing for many cancer sites. Again, this may increase the risk of cumulative toxicities.
3. There is a clear trend towards organ sparing approaches in oncology. Such approaches often need intensification of radio(chemo)therapy but, at the same time, need to decrease toxicity.
4. In the age of molecular oncology, new molecular targeting agents, which may have little or even no notable antitumoral properties themselves, will be increasingly used to improve the curative potential of radio(chemo)therapy. Therefore, clinical trials on new molecular approaches combined with radiotherapy need very high-quality and standardised radiotherapy approaches and to validate efficacy of the drugs [30]. Miss of a proportion of the cancer stem cells during part of the fractions might offset the benefit of a novel substance. An active novel drug may thereby not be selected, i.e. important opportunities could be missed. In addition, despite of their "selective" mechanisms, all targeted drugs will potentially increase

the risk of normal tissue damage, which again need highest quality conformal radiotherapy techniques for safe clinical trials.

5. New beams (protons, ions) will become increasingly available for radiotherapy in the coming years. The potential of such beams can only be scientifically tested in clinical outcome studies if combined with state of the art treatment planning, monitoring and adapting techniques [31,32].
6. Radiotherapy is currently prescribed based on broad clinical parameters such as TNM stage, histology, tumour location and volume-dose-tolerence parameters for normal tissues. Using image-based techniques individualization of the treatment is based on the (changing) anatomy of the patient. In the future, individualization will also depend on biomarkers which predict the chance of local control and of normal tissue damage. For radiotherapy biological imaging techniques that may depict the biological features of the tumour and the normal tissues in situ are anticipated to play an increasingly important role [33–42]. Sophisticated IGRT techniques will be necessary for meaningful integration of such information into biologically adapted radiation treatments.

It is foreseeable that the professionals in the field of radiation oncology but also patient advocacy groups, media and industry will bring forward these arguments for further advancement of IGRT, thereby, as outlined above, increasing the costs for the radiotherapy departments. It is equally foreseeable that in many instances these increased costs will not be followed by adequately increased budgets for investments and re-imbursements for treatment. This leads us to the true core of the question of cost-effectiveness of IGRT, namely for which specific patient and for which specific situation IGRT should be prescribed. It is obvious that not all medical novelties can be offered to all patients. Each Euro can be spent only once, and investment into one treatment therefore often is a decision against another, perhaps better approach. Enthusiasm for a novel technology should be the basis for its scientifically sound, academic evaluation but not be the basis for its general introduction into routine clinical practice [32,43]. For IGRT as for all other developments in the field of radiation oncology, all patients should have guaranteed access to technological advances if they profit from this technology. Large and high quality prospective data bases, and models which relate details of the patient (if possible including tumour and normal tissue biobanking) with details of the treatment and detailed outcome parameters, are necessary for supporting rationale decision making. For this it is a great advantage that radiobiology and radiotherapy are highly quantitative sciences and that radiation dose can be measured with great accuracy. The question whether the results were obtained from randomized trials or not will eventually lose much of its current attention if it can be demonstrated that the models in use can validly and reliably predict outcome, thereby supporting decision making and individualization of therapy.

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