Selection of external beam radiotherapy approaches for precise and accurate cancer treatment

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ABSTRACT

Physically precise external-beam radiotherapy (EBRT) technologies may not translate to the best outcome in individual patients. On the other hand, clinical considerations alone are often insufficient to guide the selection of a specific EBRT approach in patients. We examine the ways in which to compare different EBRT approaches based on physical, biological and clinical considerations, and how they can be enhanced with the addition of biophysical models and machine-learning strategies. The process of selecting an EBRT modality is expected to improve in tandem with knowledge-based treatment planning.

Keywords: external-beam radiotherapy; adaptive radiotherapy; particle beam therapy; model-based approach; machine learning; knowledge-based treatment planning

INTRODUCTION

Recently, there have been a variety of external-beam radiotherapy (EBRT) technologies employed for cancer treatment, and the number of these technologies is increasing rapidly over the years. However, physically precise EBRT may not translate to the best outcome for an individual patient. Clinical considerations alone are often insufficient for guiding the selection of a specific EBRT approach in patients. Other considerations are needed for this purpose. These include the physical dose distribution, the biological impact of the treatment on the tumor and on normal tissues, the patient’s quality of life, the cost of the therapy and its impact on the society. Considerations guiding EBRT selections can be grouped into eight categories as shown in Fig. 1.

The dose distribution of the radiation beams and the different technologies for tumor localization and for dose adaptation are fundamental factors in EBRT planning and delivery. At the same time, the dose prescription and the selected fractionation schedule must be appropriate from the biological and clinical standpoints. The predicted tumor control rate, normal tissue complication probability, and long-term quality of life need to be optimized. Social and economic appropriateness are also required to be estimated: the physical precision and accuracy are largely proportional to the cost of the EBRT, but the relationship between biological/clinical benefits and costs is often uncertain. Even when predicted tumor control rates are the same, there can exist a large difference in other aspects, as exemplified in Fig. 1.

Precise and accurate selection of EBRT takes into account all eight parameters equally well, whereas precise but inaccurate selection primarily focuses on the physical properties of the radiation dose and delivery. Imprecise and inaccurate selection is the worst scenario, in which none of the parameters are taken into consideration.

Presently, the process of selecting an EBRT modality is expected to improve in tandem with knowledge-based treatment planning in addition to physical dose calculations. This can be further improved with the addition of biophysical models and machine learning from...
real-world data. In this review, we examine the ways to compare different EBRT approaches based on physical, biological and clinical considerations and consider how they can be enhanced by the addition of biophysical models and machine-learning strategies. It is our hope that this review will provide basic information about the ways to select EBRT methods and highlight the areas where there is a strong need for the development of international standards and/or consensus.

**PHYSICAL CONSIDERATIONS**

**Primary dose distribution**

A number of technologies can be used to shape the radiation beam in order to reduce unnecessary radiation to the surrounding normal tissue and to ensure a sufficient dose delivery to the target [1]. During the megavoltage era, the development of the multi-leaf collimator (MLC) in conjunction with CT-based treatment planning allowed for conformal delivery of X-rays in 3D (3DCRT), resulting in less dosage to organs at risk (OARs) compared with 2D radiotherapy [2, 3]. Software development for inverse planning led to the implementation of intensity-modulated radiotherapy (IMRT) and volume-modulated arc radiotherapy (VMAT), which improved dose conformity and uniformity compared with 3DCRT [4–6]. Non-coplanar irradiation added further dose conformity for certain intracranial and extracranial locations [7–11]. Dose sculpting was further enhanced by proton beam therapy (PBT) and carbon ion beam therapy (CBT) through the utilization of the Bragg peak effect [12, 13]. In these EBRT delivery approaches, a spatial dose metric, such as comparing the different dose-volume histograms (DVHs) for the different radiation treatment procedures, informs the treating physicians of the physical advantages and disadvantages for each approach. Comparisons using a specific dose, such as the mean dose of an OAR \( D_{\text{mean}} \), or specific volume \( V_{\text{D}} \) that receives the threshold dose \( D \) or exceeds \( D \), using a histogram-reduction algorithm can also be used to compare two different EBRT plans with strictly physical considerations [14].

**Physical localization**

Technologies to localize the target volume precisely and accurately in the treatment position are increasingly important but expensive. Similar to stereotactic radiotherapy (SRT) for intracranial lesions, stereotactic body radiotherapy (SBRT) utilizes technologies to minimize uncertainties in the localization of tumors and normal tissues during treatment; these include body immobilization systems for securing the position of the body during treatment, and/or X-ray image-guided radiotherapy (X-IGRT) technology, in which registration of images from the planning CT and at the start of radiation treatment is required [15, 16]. The improvement in set-up errors is often used to compare the performance of the different localization technologies [17]. Dose–population histograms are used in the calculation of systematic and random set-up errors based on static internal structure components (bones, metallic markers) [18]. In general, SBRT in conjunction with IGRT, which yields smaller systematic and random set-up errors, can deliver highly precise radiation treatment for static internal structures. The precision and accuracy of this approach can be tested in static phantoms and validated in clinical studies with a relatively small number of patients, based on international standards such as IEC 60601–2-68 or academic recommendations.

**Physical adaptation**

Technologies to account for changes in the location of the target during treatment are also important. Since the respiratory amplitudes and the baseline shifts in the tumor location during the treatment cannot be accurately predicted before the actual treatment, technologies for real-time monitoring of patient anatomy and physiology during radiation delivery is increasingly utilized (Fig. 2). This is known as adaptive radiotherapy (ART), and it employs real-time monitoring information to change the treatment parameters in order to reduce uncertainties during the course of the treatment [19]. Expensive online imaging devices such as cone-beam computed tomography (CBCT) or megavoltage CT are mounted on the linear accelerators to track interfractional anatomical changes in ART [20, 21]. Real-time ART in 4D radiotherapy (4DRT) has improved the temporal precision in radiation delivery [22, 23]. Gating [24, 25] and beam tracking have become available [26, 27] for motion management. Real-time tumor-tracking radiotherapy (RTRT), in which the radiation beam is set to irradiate only when a marker is in or near the target (within \( \pm 1–2 \text{ mm} \) of the planned position), is another form of real-time ART [28]. Real-time-image gated proton therapy (RGPT) [29] is now available to reduce interplay effects in spot scanning PBT as in RTRT [30]. In-room magnetic resonance imaging (MRI) is expected to improve real-time volumetric ART for certain tumors, such as those in the liver or in the head and neck [31–33]. Despite the high cost of these technological improvements, there are presently no internationally accepted ways with which to compare different EBRT plans or approaches for ART except for the general recommendations from academic institutions [34, 35]. The dose–population histogram method that is usually used in IGRT for static target volumes is insufficient. Residual risks associated with motion coordination between the monitoring devices and EBRT must be evaluated systematically. For example, the latency between motion detection and the start or stop of the radiation beam needs to be compared using internationally agreed tests. A
standardized dynamic phantom and software to reproduce complex and irregular organ motions and changes in the body should be vigorously investigated. No clinical validation study has been reported on a reasonable way to compare different ART technologies because of the lack of a basic consensus.

**BIOLOGICAL CONSIDERATIONS**

A comparison of different EBRT approaches based on biological considerations is likewise an important issue. The joint ICRU-IAEA Report recommends using a factor of 1.1 to calculate the ‘relative biological effectiveness (RBE)’ of proton therapy \[36\] compared with photon therapy. However, it is now apparent that the RBE may be as high as 1.5–1.8 at the distal end of the spread-out Bragg peak \[37\]. For heavier ions (e.g. carbon ions), the situation is more complex because the RBE varies markedly with the particle type, the beam energy, and the depth in tissues \[38\]. International consensus on how to measure and compare inter- and intra-target variations in RBE is urgently needed for the optimal application of particle beam therapies \[36\].

Histogram-reduction algorithms have been proposed for comparing photon and particle beam therapies \[14\]. However, it may be erroneous to use the D\(_0\) or V\(_T\) when comparing extremely different dose distributions (small volume and high local doses compared with large volume and low uniform doses) when estimating biological effects \[39\]. A generalized equivalent uniform dose (gEUD) has been shown to be useful when comparing different dose fractionation schedules in the 3DRTP era \[40, 41\]. Still, it may be erroneous to use an gEUD when comparing extremely different fractionations and/or different volumes.

In EBRT’s such as SRT, SBRT, PBT and CBT, we tend to use single-treatment or hypofractionation schedules due to the laborious preparation and treatment process, high maintenance cost of the facility, and reimbursement schedule. However, hypofractionation may not be the best approach for all tumors. For example, hypofractionation can severely damage serial OARs and produce fatal adverse effects with central lung tumors \[42\], whereas it yields minimal damage to peripheral lung tumors. Therefore, internationally accepted normal tissue constraints for hypofractionation treatment are urgently warranted in EBRT. A novel formula using a linear–quadratic biological model for determining appropriate dose and fractionation based on cancer cell survival fraction and 3D dose distribution was recently introduced \[43\]. The proposed formula predicts that a more fractionated schedule is desirable for tumors in the central parts of the lungs, and that hypofractionation is good for peripheral lung tumors \[44\]. There are few other studies that take into account radiation dose distribution in the fractionation schedule \[45\], but knowledge about the clinical impact of these models is still very limited.

Genomics, radiomics and radiogenomics using gene expression data and radiological images are expected to be useful for selecting the patients who would benefit from radiotherapy in general \[46–49\] and for identifying anatomic radioresistant regions where an EBRT boost may be beneficial \[50\]. Hypoxic imaging is believed to help in identifying these resistant areas, but further study is required, since the signal-to-noise ratio is still not sufficient for use in dose escalation studies, even with semiconductor positron emission tomography (PET) \[51\]. More international collaborative research is required in order to identify the best biological markers for the selection of EBRT \[52\].

**CLINICAL CONSIDERATIONS**

Well-conducted prospective clinical trials are the basic strategy for determining clinical outcomes with a new treatment. The continual reassessment method (CRM) has been shown to help in reducing the number of patients in dose escalation studies \[53–55\]. After promising Phase II studies, randomized controlled trials (RCTs) comparing a standard therapy with a new therapy is the most reliable method for identifying the optimal radiation regimen for a tumor site \[56, 57\]. For example, RCTs of SRT with or without whole brain irradiation (WBI) have contributed to changing the guidelines for brain metastasis from upfront WBI to SRT \[58, 59\].

However, there are a number of obstacles in conducting and interpreting RCTs. First, some late radiation-related complications have a long latency period. Newly introduced treatments can lead to a rapid adoption in the present practice without data of late adverse reactions. On the other hand, if we use late adverse effects as the endpoint for introducing new treatments, we will have a difficult time modifying our
practice, since many treatments will be out-of-date by the time of adverse endpoint analysis. For example, the RCT of SRT ± WBI for brain metastasis showed that SRT had a similar overall survival rate to that of SRT + WBI at the initial analysis [58], with a lower risk of neurotoxicity at the following analysis [60], and a higher risk of death in lung cancer patients at the final analysis [61]. Second, new radiotherapy techniques predictably provide superior dose distributions to OARs without reducing the dose to the tumor. This raises ‘equipoise’, or balanced uncertainties for randomizing patients due to imbalance in the dose distribution. Third, the greater cost of one treatment and limited insurance reimbursement can pose a challenge for patients to access a new treatment in a RCT unless it is supported by a third party such as the vendor. This can lead to slow accruals or even early study termination. Last but not least, the RCT itself incurs substantial expenses. In summary, RCT may not always be the sole basis for selection of an EBRT approach or modality where technologies are evolving rapidly.

Non–randomized, intervention trials (non-RCTs) use external controls for interpretation and thus are subject to more confounding biases than conventional RCTs. Observational investigations can demonstrate correlations between a new treatment and an outcome, but can rarely be used to prove causation. Therefore, non-RCTs are not accepted as the basis of efficacy of new treatments except for rare diseases. In the case of rare diseases, the efficacy of a new treatment is often accepted without an RCT when the differences between the new and the standard treatments are substantial and the pathophysiology and natural course of the disease are well understood. This has led to many EBRT approaches being based on non-RCT series rather than on a RCT, even for common diseases. The lack of evidence based on RCT may be a reason for having a variety of EBRT approaches for a single disease type.

To date, comparisons between conventional and the new expensive EBRT approaches suffer from all of the abovementioned problems [62, 63]. With escalating medical cost, there is now a strong focus on cost effectiveness analysis for reimbursement of a new treatment, in addition to evaluations of superiority in clinical effectiveness and/or safety [64]. Therefore, ways to improve the gap between lack of evidence based on RCTs, lack of cost effectiveness analysis, and real-world demands for new technological advances are urgently needed in many countries. New approaches are being developed for comparative effectiveness research and implementation [65]. For example, in Japan, there is a program known as CHIKEN, in which vendors have to pay for all of the medical care incurred by a new treatment in order to show its safety prior to approval. There is also a SENSHIN-IRYO program, in which patients pay out of pocket for a newly introduced treatment while the government reimburses other parts of the medical care. Both programs, in conjunction with non-RCT data, have been used to show the superior effectiveness of a new EBRT approach in Japan.

**APPROACHES BASED ON BIOPHYSICAL MODELS**

To overcome the shortcomings of RCTs in the selection of new treatment technologies, models for predictions of treatment outcomes have been developed and investigated by the Radiation Oncology Society [52]. These theoretical biophysical models are expected to address physical, biological, clinical and social/economic issues and are expected to be useful in determining the most appropriate EBRT approach for individual disease types and sites. When a model predicts significant differences in serious adverse reactions between the two EBRT approaches, it may not be ethical to perform a RCT comparing the two technologies for such patients.

**Normal tissue complication probability**

Normal tissue complication probability (NTCP) involves the physical and biological considerations when predicting normal tissue toxicity and can be used to help in selecting the EBRT modality [66, 67]. Typical examples of NTCP models are the Lyman–Kutcher–Burman (LKB) model [68, 69], critical volume models for parallel structure [70], models for serial structure [71], and multivariate models [72, 73].

Confidence intervals (CIs) of the predicted values and sufficiency of fit should be confirmed for a reliable prediction in a model-based approach. Seppenwoolde et al. have succeeded in evaluating the different NTCP models for predicting the results for radiation pneumonitis (RP), giving CIs around the fitted values and the maximum log likelihood value for each model [39]. Using the data from 382 patients, they found that NTCP models using the mean lung dose (MLD) or V13Gy (volume receiving 13 Gy or more) were useful for predicting the risk of RP. Similar studies are producing important findings about RP [74, 75]. The uncertainty in a NTCP value can be calculated using a model such as LKB with more than two parameters when comparing extremely different types of dose distributions [39]. Important reports about late adverse reactions of EBRT are increasing [76–78], but they are limited in providing reliable parameters for NTCP because the incidence of serious late adverse events is usually very small.

For the comparison between photon and particle beam therapy, differences in NTCP between the two treatment technologies calculated by the LKB model may be useful in the selection of technology (Fig. 3), although the CI and sufficiency of fit are not always available [79, 80].

![Fig. 3. Concept of the statistical comparison between photon and particle beam therapy using differences in the NTCP based on the mean dose of an organ [with confidence intervals (CIs)].](image)
It is well known that the probability of complications may be affected by multiple clinical prognostic factors such as diabetes, smoking, age, anemia and gender, as well as treatments. El Naqa et al. have proposed a multivariable NTCP model to include a mixture of clinical as well as dose–volume factors using a logistic regression framework [72]. They proposed a data-mining and model-building approach with a forward variable selection based on information theory and data re-sampling approaches such as bootstrap and cross-validation methods. In their proposal, correlation measures [72] or likelihood criteria [81] for identifying pertinent variables, and the area under the curve (AUC) are used to measure the performance of the models. Christianen et al. have studied 354 consecutive head and neck cancer patients treated with photon therapy and showed the applicability of the multivariate approach for finding an NTCP model for specific adverse events [81]. They suggest that a combination of nomograms with the multivariate approach allowed for an integration of different prognostic variables in estimating the risk of radiation-induced adverse events in individual patients.

An NTCP-based approach has been exhaustively investigated in selecting patients for PBT in the Netherlands [82, 83]. A two-phase approach was used: Phase α and Phase β. In Phase α, which develops model-based indications, there are three steps: step (1) NTCP model development with prospective data collection and multivariable analysis, step (2) in silico planning of comparative studies, and step (3) estimating clinical benefits and translation of dose reductions into NTCP reductions (ΔNTCP). In Phase β, clinical validation is performed using prospective observational studies. In 2015, the Dutch Society of Radiotherapy and Oncology (NVRO) reached consensus on the ΔNTCP threshold for proton therapy selection based on the Common Terminology Criteria for Adverse Events (CTCAE) grades. According to the NVRO consensus, PBT can be applied in patients with ΔNTCP reductions of 10% or more for Grade II toxicity, 5% or more for Grade III toxicity, or 2% or more for Grade IV toxicity. The Dutch Health Council and the Dutch Health Care Insurance Board has adopted these recommendations and validated the technique.

In Germany, Jakobi et al. performed in silico biological effect analysis, using NTCP models to determine whether IMRT or intensity-modulated proton therapy (IMPT) would be beneficial in head and neck cancer patients [84]. They concluded that because the benefits among individual cases differ, even in subgroups of the disease, the relative merits of the two treatments should be evaluated based on individual treatment plan comparisons for the specific individual patients.

In the USA, Blanchard et al. have raised the question of whether NTCP models, which have mostly been developed with photon therapy data, can be applied to PBT [85]. They validated the photon-derived NTCP models for head and neck cancer in 192 patients treated with PBT. Using the leave-one-out cross-validated AUC for the receiver operating characteristics curve, they found the models to be robust and they remain valid for PBT.

Bijman et al. in the Netherlands investigated the effect of uncertainties in NTCP-model coefficients based on reported CIs and dose uncertainties with model-based patient selection in 78 oropharyngeal cancer patients [86]. They found the patient selection accuracy to be >70% when only the NTCP-model uncertainty was considered. The selection accuracy decreased with increasing dose uncertainties; in cases with excessive dose uncertainties between the planned and the actual dose, the selection accuracy decreased to 60%. They concluded that model and dose uncertainties strongly influence the accuracy of model-based patient selection for PBT.

Here we wish to stress that the NTCP-based approach is starting to be used as a tool for national health insurances to decide on which EBRT modality to support in the real world. Therefore, there is an urgent need for international standardization of related NTCP models and software to ensure patients’ safety, reporting consistency and to enhance research in this area.

**Life attributable risk of secondary cancers**

Sufficient numbers of late radiation-related adverse effects have been reported in studies of atomic bomb survivors in Japan [87] and from cancer registries in the USA [88]. The risk of radiation-induced secondary malignancies after radiotherapy has been calculated using biophysical models based on these data. Schneider et al. have taken additional steps in order to develop a site-specific dose–response relationship for cancer induction using 3D dose distributions in individual patients [89]. Using the Schneider method, Tamura et al. have calculated the risks of secondary cancers after PBT and IMRT for the same children and concluded that PBT has an approximately one-third risk of secondary cancer development compared with photon therapy in Japan [90]. These results reflect the ethical difficulty of comparing proton with photon therapy in RCT for pediatric cancers. Based on these data, the Japanese national health insurance approved PBT for the treatment of pediatric cancers in April 2016. This is an example where biophysical models have obtained a broad consensus; however, further investigation is needed in order to validate the accuracy of the model in predicting secondary malignancies after radiotherapy [91].

**BIG DATA AND MACHINE-LEARNING SYSTEMS**

It is crucial to have a reliable database with sufficient information about radiotherapy physical characteristics, its biological effects and the ultimate clinical outcomes if we are to achieve continued improvements in biophysical modeling for selection of EBRT treatment approaches [67, 92]. To achieve this type of big data analysis, machine-learning algorithms and artificial intelligence are critically important [93–97]. Dean et al. have published research about NTCP modelling using spatial dose metrics and machine-learning methods in radiation treatment for head and neck cancers [98].

Data ‘farming’ is also crucial for harvesting the vast amount of data that can be used for data mining [94, 95]. A system that stores appropriate clinical data from treated patients in order to develop and refine future models for selecting optimal EBRT modality is warranted. This is especially important for particle beam therapy, where the cost-effectiveness is a serious issue to be resolved; a patient database with data regarding costs will be important. For example, the Japanese Society of Radiation Oncology (JASTRO) has started to support the development of databases for PBT and CBT. In Japan, since 2016, treatment of pediatric cancers and bone/soft tissue malignant tumors has been reimbursed by the government for PBT and CBT, respectively. All other patients are required to be treated with the same protocol for each disease (38 diseases for PBT and 20 diseases for CBT) and to be registered
into one database at the start of the treatment. All patients are required to be followed up, and serious adverse reactions of Grade III or above are to be reported to the government. To make this registration system sustainable, a patient-centered approach to assessing adverse reactions will be important [99].

These developing databases are expected to provide reliable and objective knowledge, not only for EBRT selection, but also for decision on other non-radiation-related cancer treatments such as surgery or systemic therapy. New treatment planning systems for EBRT will expand, past their main role of generating precise radiation dose calculations, to enable a broader knowledge-based planning in the future. Radiation treatment planning will become similar to a clinical decision support system (CDSS) by improving the communication with the electronic medical recording systems and the systems providing new research knowledge (Fig. 4). Machine learning will be used to facilitate the transfer of knowledge in the CDSS. In addition, the overall care coordination support for each cancer patient requires consideration of his/her social and economic circumstances in addition to the clinical picture. A care coordination arrangement may well be combined with the radiation treatment planning system because of the role of both as a CDSS for accurate cancer treatments in different societies and organizations.

**CONFLICT OF INTEREST**

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