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Review

"Radiobiology of Proton Therapy": Results of an international expert workshop

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ABSTRACT

The physical properties of proton beams offer the potential to reduce toxicity in tumor-adjacent normal tissues. Toward this end, the number of proton radiotherapy facilities has steeply increased over the last 10–15 years to currently around 70 operational centers worldwide. However, taking full advantage of the opportunities offered by proton radiation for clinical radiotherapy requires a better understanding of the radiobiological effects of protons alone or combined with drugs or immunotherapy on normal tissues and tumors. This report summarizes the main results of the international expert workshop "Radiobiology of Proton Therapy" that was held in November 2016 in Dresden.

It addresses the major topics (1) relative biological effectiveness (RBE) in proton beam therapy, (2) interaction of proton radiobiology with radiation physics in current treatment planning, (3) biological effects in proton therapy combined with systemic treatments, and (4) testing biological effects of protons in clinical trials.

Finally, important research avenues for improvement of proton radiotherapy based on radiobiological knowledge are identified. The clinical distribution of radiobiological effectiveness of protons alone or in combination with systemic chemo- or immunotherapies as well as patient stratification based on biomarker expressions are key to reach the full potential of proton beam therapy. Dedicated preclinical experiments, innovative clinical trial designs, and large high-quality data repositories will be most important to achieve this goal.

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Introduction

While the use of proton beam radiation therapy for cancer started more than 60 years ago, the number of proton radiotherapy facilities has steeply increased over the last 10–15 years to currently around 70 operational centers worldwide. The physical

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properties of proton beams, that are a focused delivery of radiation at the Bragg peak, with very steep decline of the radiation dose behind the target volume, offer the possibility potentially to reduce toxicity by reducing the dose to adjacent normal tissues. However, biological effects of proton therapy, in particular the potential impact of their increased effectiveness, are much less well understood than those of photons. This is partly due to a limited number of proton centers that have a dedicated and well-equipped experimental area to perform the necessary preclinical experiments, but also due to a lack of systematic collection of high-quality experimental data. Worldwide more than 150,000 patients have been treated with protons, but there is still a lack of high-quality outcomes data for this radiation modality. Taking full advantage of the opportunities offered by proton radiation for clinical radiotherapy requires a better understanding of the radiobiological effects of protons alone or combined with drugs or immunotherapy on normal tissues and tumors. In order to define the current status of knowledge and evidence and to derive the most important open questions for proton radiobiology research for the coming years, an international expert workshop "Radiobiology of Proton Therapy" was held in November 2016 in Dresden. Workshop participants are listed under "Acknowledgements". This report summarizes the main results of this workshop.

RBE dependence and experimental RBE data

Physical properties of proton irradiation

The clinical use of proton beams is motivated by higher dose conformity to the target volume compared to conventional radiation and consequently their potential for dose reduction in normal tissue and therapy with high-energy photon beams [1–6]. Protons moving through tissue are slowed down and lose energy mainly by a large number of Coulomb interactions with the atomic electrons and a much smaller number of nuclear interactions, resulting in energy (dose) deposition in the tissue along the proton path. The loss of energy per unit path length, i.e., the linear energy transfer (LET), depends on the velocity of the proton and increases with penetration depth: initially, over a longer distance, it increases slowly and then, toward the end of the proton track, rapidly. Accordingly, proton beams deposit relatively low doses in the entrance channel in front of a tumor and most of their energy over a well-defined narrow region near the end of range of Bragg peak. The position of the Bragg peak varies as a function of the initial beam energy, allowing for placing the dose maximum inside the target volume. In clinical applications, the target volume substantially exceeds the width of the Bragg peak of mono-energetic proton beams. Several beams of different energies are superimposed either by passive scattering or active beam scanning techniques to deliver the prescribed dose throughout the entire target volume in depth producing a spread-out Bragg peak (SOBP) [7]. As a result, the dose in the distal part of the SOBP is deposited by a relatively larger portion of lower energy and, therefore, higher LET protons (Fig. 1), while the dose in the proximal part is deposited mostly by protons that have a higher energy and thus lower LET [8]. Also, the distribution of LET along the penetration path of a clinical proton beam varies with the widths and position of the SOBP in the patient. For intensity-modulated proton therapy, it is intended that the combined dose distributions from all beams are homogeneous in the target while the dose and LET distributions per beam in the target volume may be highly heterogeneous.

Relative biological effectiveness of protons

Apart from total absorbed dose, the radiation-induced biological response depends on various physical and biological parameters such as radiation type, dose rate, dose fractionation, dose distribution, cell and tissue type, microenvironment including oxygenation level, and the biological endpoint [9]. Current clinical experience in radiotherapy almost completely relies on data from high-energy photon therapy. In order to account for a higher effectiveness of proton beams as compared to conventional photon therapy, the relative biological effectiveness (RBE) is used. By definition, the RBE is given as the ratio of doses of a reference relative to a test irradiation, respectively, producing the same biological radiation effect. Current clinical practice, recommended by the International Commission on Radiation Units and Measurements (ICRU) [10], uses a constant RBE value of 1.1 for proton therapy in all tissues and across the entire irradiated volume, irrespective of the dose and LET. This consensus value is based on measured *in vivo* RBE data (mostly from the 1970s) at the center of the SOBP. However, a number of have investigations demonstrated variable RBE values in different test systems. This observation challenges the use of a single approximate RBE value for protons in clinical practice.

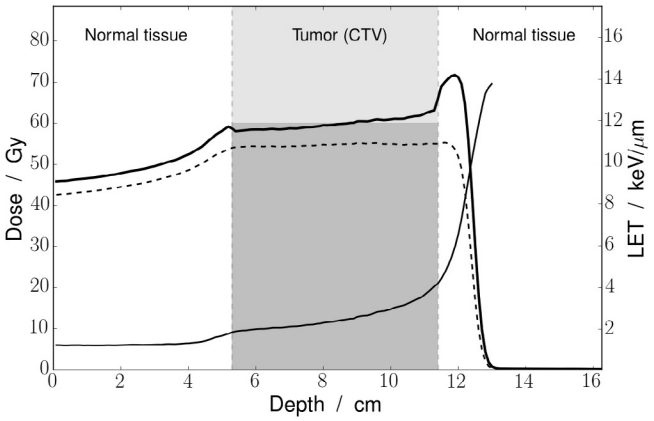

Fig. 1. Physical dose (dashed line) and dose-averaged linear energy transfer (LET) (solid line) for a clinical proton treatment field that considers physical uncertainty margins. The effective biological dose (bold line) was calculated by multiplying the physical dose with experimental dose- and LET-dependent *in vitro* RBE data [89] for tumor and normal cells within the tumor and the normal tissue, respectively.

Variation of RBE – available data

A large amount of data is available (see, e.g., the reviews by [9,11]) showing large variations and considerable uncertainties in proton RBE values. RBE values for clonogenic cell survival *in vitro* indicate a substantial spread between different cell lines. In general, RBE increases with increasing LET. An increase in LET, as observed for protons along the beam path, does not occur in photon therapy, where the LET is essentially constant. Hence, proton irradiation is more biologically effective than high-energy photons.

RBE averaged over a large number of cell lines increases with increasing dose-averaged LET and thus with depth in a typical SOBP from about 1.1 in the entrance region, to about 1.15 in the center of the SOBP, about 1.35 at the distal edge and about 1.7 in the distal dose fall-off region [11]. Furthermore, there is a trend toward increasing RBE as the α/β ratio (a parameter of the linear quadratic model inversely related to fractionation sensitivity of a biological endpoint) decreases. Moreover, *in vitro* data show an increase in RBE as dose per fraction is lowered [12,13]. There is a great need for *in vivo* experiments on normal tissues and tumors under well-defined conditions to define *in vivo* RBE values but also to unravel molecular mechanisms of radiobiological efficacy of proton beams. RBE data for clinical endpoints are presently too sparse to allow recommendations of RBE values in specific clinical

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situations that differ from a value of about 1.1. For clinical use, however, the patient-specific LET distribution may be taken as a surrogate for RBE distribution and may be considered in radiation treatment planning, see Section 2.

Time structure and dose rate dependence of RBE

RBE depends on physical factors such as dose rate, the number of pulses, time interval between pulses, and dose per pulse. Studies using photons and electrons at ultra-high dose rates (e.g. 10^{10} Gy/min) have shown increased cell survival after doses of several Gy and hypothesized that this is due to oxygen depletion and/or radical–radical recombination lowering the efficiency of the pulsed radiation. Recent studies using *in vitro* tumor cells and xenotransplanted tumors in mice, and comparing pulsed and continuous 20 MeV proton beams from a tandem accelerator revealed no evidence for a substantial change in radiation response by exposure with single pulses of few Gy at ultra-high dose rate and 1 ns duration [14–16]. However, contradictory data suggest reduced normal tissue complications with unchanged efficiency in tumor growth delay after irradiation of xenografts with short electron pulses of high dose rate ($\leq$500 ms, $\geq$2.4 kGy/min) compared to conventional dose rate exposure ($\leq$1.8 Gy/min) [17]. These findings clearly indicate a need for more research on dose rate effects, which could reach clinical relevance for new synchro-cyclotrons, which can deliver therapeutic proton doses in microsecond time intervals.

Link from experimental to clinical data

In clinical datasets, there are indications that the RBE increases throughout the SOBP but in most cases the difference from the value of 1.1 is not substantially significant [18]. A recent study provides clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma by correlating post-treatment MR image changes with dose and increased LET [19]. However, the pronounced RBE increase at the distal edge of the Bragg peak seen *in vitro* (e.g. [20,21] with RBE values exceeding 2.0) is not evident from most clinical data. Potential reasons are the smearing out of higher LET components in extended targets due to range straggling and uncertainty, organ motion, anatomy and positioning variations, dose–volume effects, tissue heterogeneity, microenvironmental changes, etc.

Relevant experimental models and endpoints

Translation of knowledge on proton radiobiology to the clinic still requires more insight in RBE, in particular *in vivo* data on normal tissue effects. *In vivo* endpoints of clinical interest are inflammation, standardized cognitive tests and late tissue reactions such as the radiation-induced myelopathy in spinal cord models (e.g. [22]) or brain necrosis. The predicted deviation of radiation effects based on variable RBE compared to RBE of 1.1 is expected to be highest for late responding tissues (low α/β) distally to the target region that receive low to intermediate radiation doses. Why these effects do not necessarily lead to clinically detectable changes will be discussed below. While a direct extrapolation of *in vitro* data to humans is impossible, preclinical experiments can be used to test mechanistic hypotheses. A panel of tumor and normal tissue cell lines with varying radiosensitivity should be defined and used to learn more about variations between cell lines. New three dimensional *in vitro* models including organoids (e.g. micro-brains) are attractive options for such investigations. Other biological effects of interest, such as data on gene expression, protein expression, etc., are currently emerging. Experimental studies have limitations due to the lifespan of the animal, e.g., for detection of secondary neoplasms. The risk of secondary cancer induction should, therefore, be analyzed based on clinical data from population based registries. Basic physical parameters are radiation dose, LET, and volume that can be derived from treatment plans.

Reference irradiation

While it is essential to improve the accuracy of experimental RBE data, it is important to understand that, first, RBE quantifies the effectiveness relative to a reference irradiation and, second, significant RBE uncertainty can originate from the reference. To obtain RBE values as well as the underlying photon dose–response curves, different types of reference photon conditions are in use, ranging from mega-voltage photons to kilo-voltage X-rays. However, different photon energies also imply different LET values: a decrease in photon energy and thereby energy of the secondary electrons results in an increased LET. Accordingly, the comparison of two proton RBE values obtained with different reference radiation qualities requires at least a normalization of the LET of the two reference radiation qualities. Nevertheless, for future experiments clinical high-energy reference radiation is recommended, with 6 MV photons being the clinically most relevant radiation source. Where no 6 MV accelerator is available for large scale radiobiology experiments comparing protons and photons, it is recommended that the experimental photon beam (often 200–250 kV X-rays) is standardized with regard to energy spectrum as well as dose rate and normalized to the results obtained with 6 MV linear accelerators in exactly the same experimental systems. Additionally, the experimental proton beam needs to be standardized according to energy and dose rate for comparative experiments aiming to estimate RBE.

Treatment technique

Potential differences in RBE between actively scanned beams and passively scattered beams [23] can be ascribed to physical parameters. Differences in LET distribution of the mixed radiation field can occur within an SOBP and, in particular, for intensity-modulated proton therapy plans with the same dose. Differences in the dose distribution may result from primary and secondary particles with, e.g., more shallow distal dose fall-off and more neutrons in scattered beams. Pencil beam scanning and passively scattered beams rely on different uncertainty and margin concepts which may lead, especially, for moving targets to different volume effects. An increasing number of proton therapy centers are starting to treat patients using scanned beams.

Modeling RBE

Reliable models for predicting biological radiation effects as a function of LET would allow for including variable RBE in treatment planning. Simple phenomenological models (e.g. [24]), in general, do not account for the non-linear RBE variability as function of dose, LET and tissue endpoint. More elaborate models consider the dose deposition by the secondary electrons in more detail based on track structure theory (e.g. the local effect model [25]). Apart from the dependence on dose and beam quality, models developed over the last decades also differ in the description of the biology. Some approaches model the processes of DNA damage and repair in great detail [26]. On the other hand, the RBE models already in clinical use for carbon ion therapy, such as the local effect model I (LEM I) [27,28] and the microdosimetric kinetic model (MKM) [29,30], determine the RBE based on the radiation response after photon irradiation. But even the most advanced models need to be further improved to account for dose fractionation in advanced radiotherapy schedules. A general problem is the lack of relevant *in vivo* data that could serve as input parameters

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for the models as well as clinical data for benchmarking and validating the models.

Interactions of physics and biology for today's treatment planning with protons

Current status and clinical perspective

From a clinical perspective, the current discussion on the interaction between physics and biology focuses on the choice of a suitable RBE model, on normal tissue effects (less on tumor control), and the question whether there is clinical evidence for an increased biological effect of protons in some situations.

The simplest RBE model to describe the difference in the biological effect of protons compared to photons is to assume a fixed value of RBE = 1.1. Currently, proton radiotherapy centers stick to this model for a number of reasons: (1) over 150,000 patients have been treated with this RBE model with no undue toxicities, (2) it simplifies clinical routine and makes it less error prone, (3) helps to compare clinical data obtained in different centers, and (4) leads to greater consistency between proton centers regarding the RBE effect. Although it has been recognized that a constant RBE does not reflect the RBE dependence on tissue type, dose, dose per fraction, position in the SOBP, study endpoints, etc., it was concluded that variations of proton RBE with these parameters in clinical situations are small relative to the current resolution of clinical outcome data.

High level clinical evidence that results from randomized cohort studies or systematic reviews of clinical outcome data and demonstrates a clinically relevant variation of proton RBE is still missing. There is, however, an increasing body of evidence for an increased biological effectiveness toward the distal edge of the treatment field from clinical case studies and mostly small patient series [18]. Significant RBE variation was found in studies using radiological endpoints [19,31], which are more suitable for resolving a spatially non-uniform response within the target volume. For example, for pediatric ependymoma patients, the dose level that results in a 50% probability to observe an image change in a follow-up magnetic resonance imaging (MRI) voxel was significantly correlated with the dose and LET values in that voxel [19]. The analyzed clinical data suggest that the threshold dose to observe an image change decreases linearly with increasing LET.

An increase in normal tissue toxicities at the distal edges of the treatment fields is particularly relevant for the irradiation of tumors of the central nervous system (CNS). Typically, less straggling of the proton ranges occurs for these treatments due to more superficially seated tumors, high tissue homogeneity and high positioning accuracy, leading to sharp Bragg peaks and high LET values.

It is important to realize that an RBE increase at the distal field edge translates in an extension of the biological-effective range of the treatment field by up to a few millimeters beyond the distal edge of the target volume. This biological range extension and the inherently elevated RBE should be considered during treatment planning. To reduce the risk of a potential increased detrimental biological effect, it is common practice to keep high-LET regions away from critical normal-tissue structures, e.g., by adapting beam angles. At present, the clinical practice of using a fixed RBE of 1.1 cannot be abandoned based on high-quality evidence favoring other values in specific situations.

Why don't we see the preclinical effects in the clinics?

Given the clear experimental evidence for a variable biological effect of proton irradiation in *in vitro* as well as *in vivo* (cf. previous section), the question arises why this effect in less apparent in cancer patients managed with proton therapy. An obvious reason might be that preclinical experiments are designed to test such an effect while the aim of the clinical treatment planning process is to reduce the risk of such side effects, for example through beam angle adaptation to avoid placement of high-LET regions in critical normal tissues. Furthermore, the absolute dose in regions with an enhanced RBE effect may be well below local tolerance e.g. in the low-dose part of a marginal dose fall-off. Also, the effect of an increased RBE is expected to be confined to a (sub-) volume within the irradiated volume. Therefore, the relative size of the radiobiologically more effective region can be expected to decrease with increasing treatment volume, i.e., the effect is smeared out. On top of all this, and perhaps most importantly, clinical case series are subject to a large patient-to-patient heterogeneity of treatment effect. Thus, the effective spatial variability in RBE will be smeared by variations in dose distributions, anatomical variations, motion during delivery, variation in setup between dose fractions, and patient level factors such as comorbidity or co-medication. This will drive up the sample size required to show a statistically significant effect of varying RBE. However, large clinical trials are in progress and large registries are being created that may provide sufficient statistical power to estimate RBE at a clinically relevant effect size.

Despite the current lack of high-level clinical evidence for a variable RBE, general agreement exists on the following fact: with an increasing capability to accurately deliver the dose as given in the treatment plan (using techniques such as proton range verification, high-precision patient positioning and image-guided adaptive radiotherapy), the proton Bragg peaks will be positioned in each fraction more and more precisely at the same spot. This results in repeated exposure of tissue with steeper dose gradients as well as areas with elevated LET values. As a consequence, the smear-out effect of the RBE is expected to become smaller and RBE may increase locally. The enhanced physical precision may also allow for stopping proton beams directly in front of organs at risk to fully utilize the potential of proton therapy. These desirable advances in high-precision proton delivery will definitely increase the importance of a careful and robust modeling of RBE in the context of treatment planning. A continuous assessment of clinical data will be necessary to show whether the simple fixed RBE of 1.1 remains sufficient for patient treatment.

Counter measures against uncertainties related to RBE

The first step to improve the description of the impact of physics on biology in treatment planning is to characterize the radiation field in an appropriate way. The absorbed dose alone seems insufficient and another quantity that parametrizes the beam quality is necessary. Currently, LET – which is accessible by simulation and importantly by measurement – is the most commonly used beam quality parameter. However, standard treatment planning systems (TPS) do not provide information on LET. A logical next step is therefore to make maps of three dimensional LET distributions available in the TPS for each treatment plan – side by side to the optimized dose distribution (Fig. 2). While such an LET visualization could be implemented immediately in a TPS, its routine use is currently still hampered by the demands on computational power.

A visualization of the LET distribution in the treatment planning process can be used in several ways:

a) Visual plan evaluation: reject treatment plans with increased uncertainty due to unfavorable LET distribution during plan approval;
b) Selection of beam configurations: choose appropriate beam angles during treatment planning;

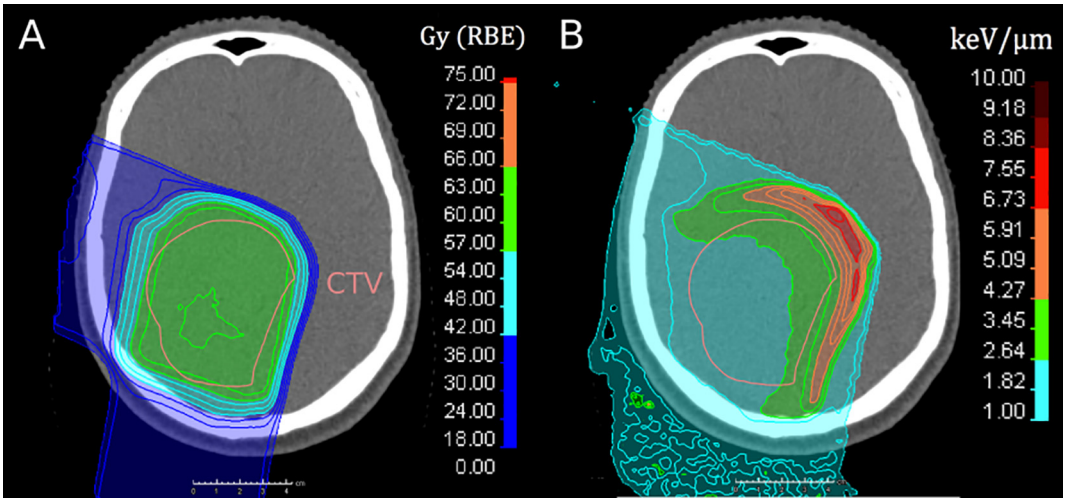

Fig. 2. Computed tomography of a brain tumor patient treated with proton therapy overlaid with the (A) dose and (B) dose-averaged LET distribution. The treatment plan was recalculated using a Monte-Carlo simulation that was adapted and commissioned for the University Proton Therapy Dresden. Courtesy of Jan Eulitz, OncoRay, Dresden.

c) Redistribution of LET: after dose optimization, request TPS to provide a uniform LET distribution or to move high LET values away from organs at risk without changing the dose in the target volume [32,33] and
d) LET optimization: perform a simultaneous optimization of dose and LET to obtain a desired (constant) radiation effect throughout the target volume with minimal integral dose [34,35].

Approaches a) and b) can be understood as general measures to support decisions during the process of treatment planning and plan approval (Fig. 2). On the other hand, strategy c) requires the use of intensity-modulated proton therapy and is therefore incompatible with treatment techniques such as double scattering or planning strategies such as single field uniform dose optimization. Option d) appears primarily useful when a suitable RBE model is employed – as is routinely done in carbon ion therapy [27]. A simple product of dose and LET is insufficient for a realistic optimization of the biological effect due to the dose dependence of the RBE and because doubling the dose usually leads to a much stronger increase in biological effect than doubling the LET. Once modeling of clinical RBE with acceptable uncertainties becomes available for proton therapy, option d) may become an attractive strategy to improve biologically optimized patient treatment. Ultimately, reliable models would, in principle, allow for carrying out variable RBE-weighted dose optimization.

Potentially, robust planning to account for range uncertainties, based on reducing dose gradients, might also mitigate the variance in RBE. However, such a smearing-out approach precludes the possibility to exploit the full potential of high precision proton therapy. Another strategy to enhance the robustness against potentially increased uncertainties in the biological effect could be knowledge-based treatment planning integrated in the TPS. It might either provide some positive guidance based on best practice from experienced centers or raise a red flag in the case of a potentially risky treatment plan, e.g., end of proton track in (the near vicinity of) the spinal cord.

The aforementioned measures focus on improving the description and distribution of the applied irradiation within the patient, i.e., on physics. On the other hand, there is a lot of potential to improve the accuracy of describing the effect of proton irradiation, i.e., biology. Furthermore, a clinical data driven approach may help to bridge the gap between the knowledge on *in vitro* cell response and the missing clinical experience with a variable RBE in proton therapy. It appears possible to transfer valuable clinical experience with a variable RBE prescription gathered over more than two decades in carbon ion therapy directly to proton therapy to reduce uncertainties due to the varying biological effect [36,37]. One simple fact to be learned from carbon ion therapy is that uncertainties in the RBE values are mainly due to uncertainties in the radiation response to photons and less due to that of ions.

Biological effects of combining protons with systemic anticancer treatments

In photon radiotherapy, the standard of care for many tumor entities is the combination with sequential or concomitant administration of systemic drugs or immunotherapy. Comparative prospective clinical trials on proton versus photon radiochemotherapy are very limited and suffer from the fact that a differential efficacy may either be due to the different beam qualities or due to a different interaction of the simultaneous chemotherapeutics or immunotherapeutic strategies with protons versus photons. For example, in non-small-cell lung cancer clinical trials are performed or already finished with the aim to show reduced toxicity after combined chemotherapy with protons, as a potential basis for later radiation dose-escalation trials [38]. Due to the variety in applied proton radiation doses as well as different drugs and application schedules, a general conclusion is currently not justified [39–48]. Also, the majority of studies enrolled less than 100 patients. Nonetheless, in most cases combined chemotherapy and proton irradiation resulted in tolerable toxicities. Also for gastrointestinal tumors (stomach, esophagus, pancreas, liver), the experience of proton irradiation was recently reviewed [49]. Similar to the situation in lung cancer, overall low quality and quantity of the available data impede a direct comparison and conclusions. However, as far as retrospective comparisons to photon data are reliable, proton radiochemotherapy may offer the potential to lower treatment associated side-effects without compromising the survival in several gastrointestinal tumors.

An uncritical translation of clinical standard photon radiochemotherapy schedules into proton radiotherapy is nonetheless controversially discussed. The interaction between chemotherapy or other systemic treatments with radiotherapy may be different between photon and proton irradiation, thus potentially reducing or increasing efficacy of the combined treatment. However, so far published studies observed similar toxicities

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for treatment combinations including either photon or proton therapy.

The lower integral dose and reduced irradiated volume applied with proton compared to photon radiotherapy may not only affect the risk of second cancer, but may also decrease the immunosuppressive effect of radiotherapy due to the decrease in the detrimental effect on local immune cells [50–53]. For photons, few case reports describe the contribution of the immune system to the response of distant unirradiated tumor sites. The so called abscopal effect seems to be attributed to the release of immune-stimulatory molecules from the irradiated tumor cells, leading to immunogenic cell death of distant tumor cells [54]. Although the underlying mechanism of the abscopal effect is not fully understood and questions regarding total dose, therapy scheduling and fractionation remain, hypofractionated or stereotactic radiotherapy has been proposed to be the most appropriate modality for photons since it could lead to a more robust immune response than conventional fractionation [54,55]. The clinical efficiency of combination of immunotherapies with photon radiation has been modest so far [55]. It can only be speculated whether the inverted depth dose profile of particle therapy in general might lead to a more favorable clinical outcome when combined with immunotherapies.

Recent preclinical studies comparing DNA damage repair following photon or proton radiotherapy suggest that there are distinct differences in the choice of repair pathways and relative biological effectiveness based on repair deficiencies [56,57]. Similar studies on combined treatments are missing. Nonetheless, if these observed changes hold true for a wider variety of tumor types and systemic treatments, a biomarker based on repair deficiencies could be developed, assigning cancer patients to the appropriate radiation quality or, further along the road, into combined treatment schedules with selected DNA repair inhibitors. Also, micromilieu parameters may be affected differently by different beam qualities, with potential secondary effects on efficacy of combined treatments. The human endothelial barrier function influences the release of drugs from micro vessels in the tissue. Indications for compromised barrier function were found in human umbilical vein endothelial cells following photon but not proton irradiation [58]. This finding could have implications for the scheduling of drug application combined with proton irradiation. However, such sequence variation has not been tested in photon or proton radiotherapy and practicability remains questionable for both beam qualities.

It is still controversially discussed if low LET radiation such as protons and photons per se cause different biological effects. Assessing the interaction of protons with systemic therapies is therefore closely entangled with the underlying question of different biological mechanisms and signaling pathways differentially induced by protons and photons. Preclinical data have shown e.g. different proteome and phosphoproteome patterns after irradiation of tumor cells with either photon, proton or carbon beams [59]. It is the aim of preclinical *in vitro* and *in vivo* studies to unravel radiobiological and molecular mechanisms of the effect of proton radiotherapy and to investigate the effect of approved and particularly of unapproved drugs in combination with protons versus photons. Advanced computational models can predict the cellular survival following the application of different radiation qualities [26,37]; however, it is still not clear how these translate to patient level outcomes. Also, models for the interaction of systemic treatments and radiation are still missing. Clinical studies should focus on careful patient selection and extensive data (dosimetry, imaging, treatment plans, side effects, concomitant medication, health records, and long follow-up) and biomaterial (biopsy, re-biopsy, blood, urine, and stool) collection to accelerate biomarker driven trials in the future.

In summary, there is currently insufficient knowledge and understanding of the interaction of combined systemic drug treatments or immunotherapy with proton irradiation. Therefore, systematic pre-clinical and clinical studies of the effect of combined proton radiotherapy with standard chemotherapy, molecular targeted drugs and immunotherapies are needed to assign patients to the most efficient and least toxic treatment. Also, drugs that, due to radiosensitization in normal tissues, are highly effective but too toxic when combined with photons, may be reconsidered for testing in combination with protons, where the lower integral radiation dose may lead to reduced toxicities due to radiosensitization.

Particularities of clinical trials testing biological effects of protons

Clinical application of proton therapy

The hypothetical clinical benefit of proton over photon radiation therapy is the potential for delivering a specific dose to the tumor while sparing critical normal tissues [60–62]. First proton irradiations were performed in 1954; but a wider clinical use of proton therapy started in the 1990s in the U.S.A. [60] and nowadays in Europe. Up to now (status, March 2018), 28 centers in North America, 21 in Europe, 18 in Asia, and one in Africa have treated approximately 150,000 patients with proton radiotherapy [63]. In general, there is ongoing enthusiasm about ion beam therapies, but so far limited high-level clinical evidence is available confirming a benefit over conventional photon radiotherapy. The initiation of clinical trials to test the toxicity and effectiveness of proton irradiation will help to generate the missing clinical evidence. Unfortunately, most of the published data on proton irradiation are observational and mainly retrospective case series, often in highly selected cases, with limitations in respect to patient stratification, clinical outcome and the complex interventions of radiotherapy with many confounding and partly unknown variables [64,65]. Radiation dose plan comparisons suggest that proton therapy may not be superior for patients with broad indications e.g. localized, low-grade prostate cancer, implying a need to identify certain patient subgroups which would benefit.

Despite increasing knowledge of RBE varying by dose, fractionation schemes, the position within the beam trajectory etc., the applied RBE concept in clinical routine has not changed yet (cf. Sections 1 and 2). The main argument, besides remaining uncertainties in RBE, is pragmatic, namely to keep consistency among institutions to generate comparable results. However, if the RBE truly varies between clinical cases and from institution to institution, disregarding this variability is associated with a lack of statistical resolution when linking dose–volume fractionation effects to clinical outcomes. Further, using a fixed RBE, there is a risk of under- or overdosing the tumor or normal tissues overall or in sub-regions within these.

Is it feasible to estimate RBE for a specific endpoint from clinical trials? Definitely, yes. However, to achieve a reasonable precision of the RBE estimate, say, within a ±5% with of the 95% confidence interval may, depending on the steepness of the dose–response curve, require a trial with several thousand cases. Patient-to-patient variability in all other aspects than the two radiation modalities would need to be carefully controlled or adjusted for using statistical techniques. In the meantime, surrogate endpoints to quantify the local RBE distribution could be advanced imaging methods. Thus, regional occurrence of complications could be correlated with dose and LET maps to estimate a local RBE (cf. Section 2). Data generated from such a retrospective trial might provide guiding information with regard to patient selection in the future e.g. linking imaging information with RBE occurrences

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to enrich a study population. However, the biologically observed increase in RBE at the distal fall-off of the Bragg peak does not appear to be a dominating factor in a clinical situation otherwise it would have caused more frequent side effects in past clinical trials. As the precision of dose delivery in daily proton radiotherapy improves, the potential variation in RBE in the irradiated volume might gain importance as the Bragg peak will be placed in every fraction in the same tissue voxels.

Clinical trial design

Phase I/II clinical trials

Numerous phase I and II trials, single-arm or randomized controlled, of proton therapy – often in combination with cytotoxic or molecular targeted agents or with immunotherapy – are in progress worldwide. These are in principle not too different to similar trials with photon therapy. Phase II trials with photon delivery in the control arm, however, rise most of the concerns listed below for phase III trials.

Randomized controlled phase III trials

The level of clinical evidence for patient-level benefit of proton over photon therapy is still low although the number of proton therapy centers is increasing worldwide. A recently published overview of currently ongoing clinical trials identified 122 active proton therapy trials of which only five randomize patients between protons and state of the art photon therapy [66]. It also showed that observational studies account for only 21% of registered trials, but 71% of planned patient accrual. The major advantage of randomized controlled trials is internal validity of the treatment comparisons leading to a minimization of bias. Therefore, randomized controlled trials (RCTs) are considered the gold standard in evidence-based medicine in general as well as in radiation oncology but other study methodologies may achieve this same goal (i.e. model-based approach). Non-randomized trials are prone to patient selection bias because access to proton therapy is influenced by important prognostic factors such as general condition and potentially socioeconomic issues [67].

Patient accrual is a crucial point for RCTs in proton therapy and is influenced by costs, ethical issues, and feasibility to name a few issues. Randomization is easier if there is a real equipoise and no superiority expected. If there is any preference, acceptability can be improved by 2:1 randomization, but should not be skewed more than 3:1 to preserve statistical power. Pediatric tumors represent a special clinical situation. On the one hand, high-quality clinical data on the long-term effectiveness and toxicity associated with the use of proton beam therapy is lacking [68]. On the other hand, there is no real equipoise for many indications, as proton beam therapy reduces the radiation dose to normal tissues, e.g. the developing brain in children, which have a higher susceptibility for late radiation-induced side effects.

A major problem with RCT's when comparing protons with photons is the lack of proper inclusion criteria. A benefit of protons compared to photons in terms of prevention of radiation-induced side effects can only be expected if the dose to normal tissues can be reduced significantly with photons. This implies that patients should only be eligible for such an RCT when there is at least a predefined dose difference. If not, no benefit can be expected as recently shown in an RCT comparing photons with protons in lung cancer that failed to show a difference in radiation-pneumonitis, while no difference in the mean lung dose was observed (Figs. 3 and 4).

Barriers to RCTs comparing proton v. photon

Randomized clinical trials (RCT) provide the highest level of clinical evidence. Nevertheless, RCTs evaluating proton therapy have been limited by several factors:

(i) Some stakeholders – proton therapy centers, radiation oncologists working at these, self-referred patients – have not favored evidence-based medicine. Partly as a result, many proton therapy centers miss a clinical trials unit and other research infrastructure. In addition, some are stand-alone proton centers without access to photon radiotherapy departments.

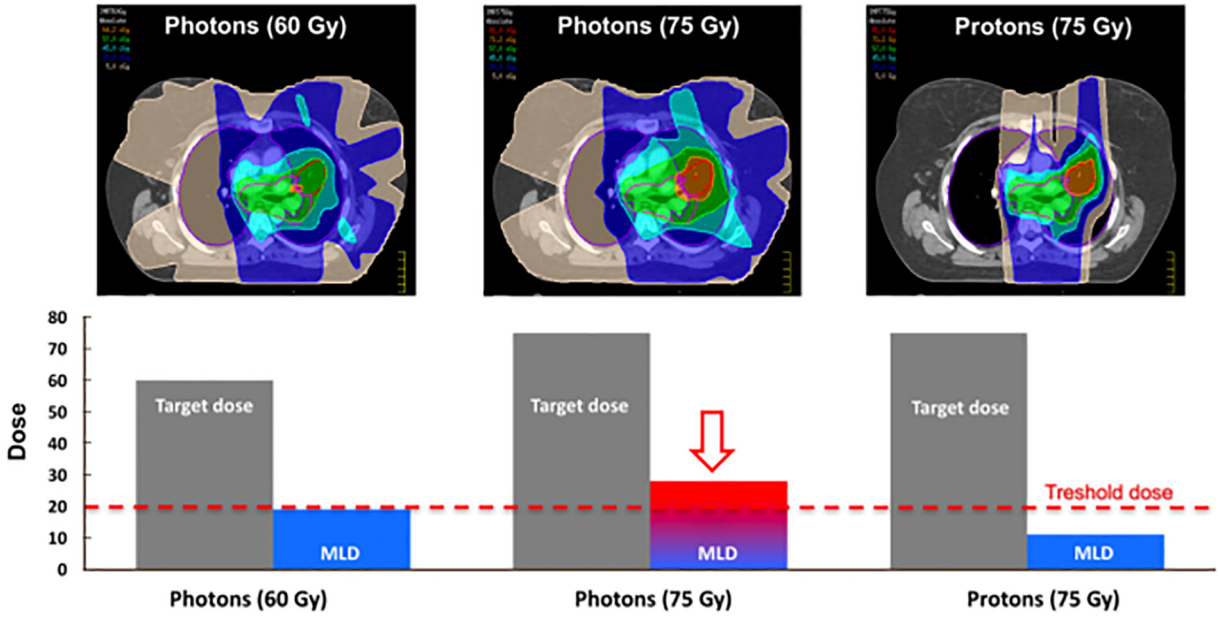

Fig. 3. Example for a proton therapy-directed randomized control trial for non-small cell lung cancer patients (NSCLC) to test the therapeutic ratio relative to photon treatment consisting of three arms: (A) current standard, 60 Gy photons; (B) dose escalation, 75 Gy photons; (C) dose escalation, 75 Gy protons. For the three arms, treatment plans as well as target dose and mean lung dose (MLD) are compared for the same patient. The proton arm aims at escalating the target dose without increasing dose to normal tissues, i.e., improving local control without increasing toxicity.

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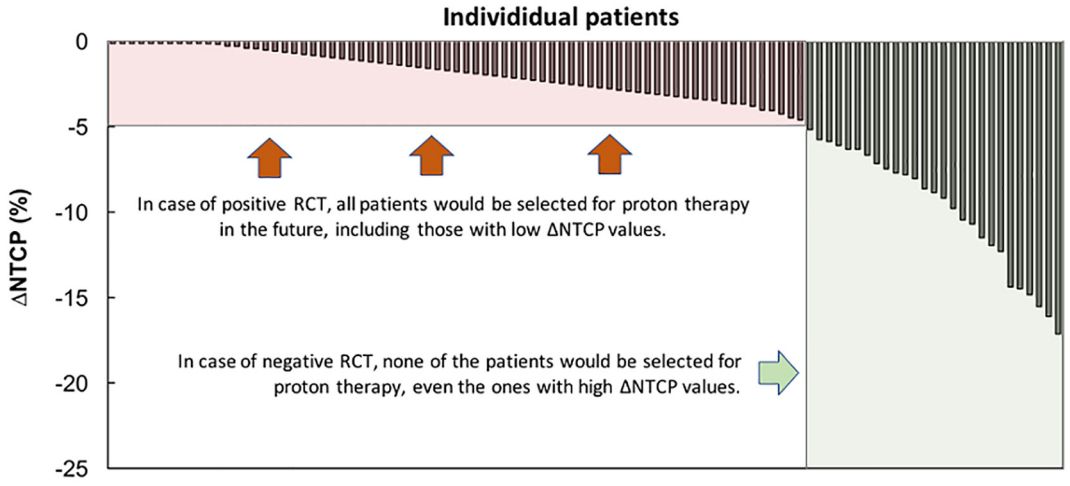

Fig. 4. In the model based approach, for each patient the normal tissue complication probability (NTCP) is modeled for a photon and a proton treatment plan. The expected patient-specific NTCP reduction ΔNTCP (NTCP difference between photon and proton plan) can be used to select patients for proton therapy and to stratify patients for a randomized clinical trial (RCT). Without stratification, RCT might lead to conclusions applied to all patients, which neglect the individual extent of the potential benefit of a proton treatment.

(ii) The proportion of patients declining to give informed consent to randomization might be higher than in other interventional trials due to explicit patient preference for proton treatment.
(iii) Lack of cost coverage by healthcare payers can lead to exclusion of otherwise eligible patients from the trial or, in some cases, can lead to selective drop out of patients from the proton arm of the trial.
(iv) Major heterogeneity among the performance of centers due to variability in equipment, standard operation procedures, and members of the team, which severely hamper generalizability of results.

There are long-standing arguments regarding the ethical requirement of equipoise in a trial of protons vs. photons. However, the general view is that there is collective equipoise in Freedman's sense of there being a considerable disagreement among informed experts regarding the magnitude of a potential difference between modalities [69]. Recent trial outcomes that have shown no clear advantage of the proton arm of actual trials have helped put these ethical concerns to rest [70].

Testing the proton therapy hypothesis

The prevailing proton therapy hypothesis is that the dosimetric benefits from treatment plan comparisons between proton and photon therapy plans convert into a clinically meaningful benefit at the patient level. It may be important to note, as discussed above, that this is not the only conceivable advantage of proton therapy, but it has dominated, and continues to dominate, much of the thinking regarding proton therapy and it may therefore be useful to consider this in more detail. First, it is absolutely necessary to compare proton radiotherapy against state of the art photon therapy with respect of treatment planning, image guidance, and adaptation. One research approach would be to apply similar target dose with lower dose to normal tissues aiming to reduce toxicity without affecting local control. Another strategy would be to escalate the target dose without increasing dose to normal tissues aiming to improve local control without increasing toxicity. In principle, it is attractive to combine both beneficial effects aiming to increase local control while reducing toxicity at the same time. Note, however, that irrespective of the chosen treatment schedules, the aim of any randomized trial of protons versus photons must be to test the therapeutic ratio of the two treatment modalities. This would mean to show superiority with respect to either tumor control or normal tissue toxicity while at the same time demonstrating non-inferiority within an appropriate margin for toxicity or tumor control, respectively, in the two situations.

This hypothesis could be tested in a smart study design using the example of non-small cell lung cancer (NSCLC). The rationale for performing a randomized controlled trial in advanced NSCLC is that many patients fail by loco-regional progression [71]. Some photon dose escalation studies showed improved efficacy concerning local control and overall survival, but the large randomized photon therapy trial, RTOG0617, did not support this hypothesis [72]. One explanation for the apparently harmful effect of higher dose is the putative dose–effect relationship between heart dose and overall survival [73,74]. A potential study design, which could answer both questions, would consist of 3 arms (Fig. 3). Interim analysis and stopping rules concerning tumor control probability (TCP) and normal tissue complication probability (NTCP) must be defined carefully.

Multicenter trials are necessary to manage recruitment in a reasonable time and to increase generalizability of the obtained results. On the downside, center variability within multicenter trials comprises difficulties so that enormous efforts in quality assurance and harmonization are required. There is already a high center-variability in intensity-modulated radiotherapy planning, which might even be higher in intensity-modulated proton therapy planning [75,76]. Both, the current position of a center on the learning curve and the motivation not to exhaust maximum constraints affect the quality of treatment plans. Furthermore, differences in treatment planning, equipment, and in-room imaging acquisition as well as various other factors such as toxicity scoring add further uncertainties. Addressing the above challenges with pragmatic solutions already at the early stage of trials will make their future translation into routine clinical practice more successful.

Use of NTCP models for patient selection in RCTs

If the aim of a trial is to test the above proton therapy hypothesis, the most informative cases are patients where the dose to normal tissues can be reduced significantly with photons. By analogy with biologically targeted therapies in the context of photon therapy, one could claim that technologies like proton therapy need to be tested in enriched cohorts which reduces the risk of false negative results [77]. If no enrichment is implemented, the trial may

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not address the hypothesis as recently shown in an RCT comparing photons with protons in lung cancer that showed no difference in radiation pneumonitis, but also showed no difference in the mean lung dose (Figs. 3 and 4) and mean esophagus dose in both treatment arms and a lower heart dose in the proton arm. Locoregional tumor control and survival as well as pneumonitis and esophagitis were similar in both arms [70]. Treatment comparisons in enriched populations are more effective and fewer patients are required. However, the recruitment phase may not be shortened as the enrichment reduces the eligible patient population since most patients will initially be referred to an institution that has only access to conventional irradiation modalities. Therefore, an efficient selection of patients to enrich study cohorts would benefit substantially from including these standard-of-care treatment centers in networks together with proton therapy centers [78]. Furthermore, a practical approach is necessary for a remote exchange of patient information relevant for patient identification between the centers [79]. Nevertheless, even negative results derived from non-enriched populations may provide useful information regarding biological questions, i.e. the RBE-question. There is the possibility of post hoc biomarker analysis, which can be hypothesis generating for future trials.

Non-randomized study designs

Randomized comparisons should be performed whenever they are feasible. However, at the very least detailed dosimetric, disease and patient characteristics should be stored in a standardized format together with detailed patient outcome data. Other trial designs like well-defined and statistically planned prospective matched pair comparisons may produce useful information

It is likely that the possible benefit of proton therapy will vary between subgroups of patients. Thus, in all prospective datasets, biomaterials for biomarker evaluations as well as diagnostic imaging and radiation treatment plans should be collected to define parameters identifying these subgroups.

Another important problem in some countries is lack of acceptance of randomization by insurance companies, which refuse to cover extra costs in patients randomized to proton therapy. It is important that the radiation oncology community keep lobbying third-party payers convincing them that it is in their best interest to support the generation of evidence regarding the indications and benefits of proton therapy. One work-around is being considered in Dresden where some so-called patient-choice protocols are performed meaning the decision for treatment modalities depends on patient preference (which is highly influenced by cost coverage of the individual insurance), e.g. Proto-Choice-Brain (ClinicalTrials.gov Identifier: NCT02824731). Such a design is not randomized and can only be expected to be with low bias if, as in Germany, health insurance is mandatory for all individuals and the insurance fees do not correlate with the acceptance of cost coverage for proton therapy by the insurance.

Centers in the Netherlands and Denmark are considering NTCP model based patient selection as an alternative to RCTs in some situations. The model based stepwise selection of patients for proton therapy in case of clinically relevant lower toxicity predicted by validated NTCP models has been accepted by the Dutch health authorities [80]. Then, the added value of protons can be validated by comparing the observed rate of toxicity as obtained by protons with the expected toxicity rates (average NTCP) based on the back up photon plans (Fig. 4). In such a design, each patient is his or her own control. Therefore, maximum efforts are required to collect and update clinical radiobiology and patient outcome data of high quality including morbidity assessments and radiotherapy dose plans for both photons and protons. These data are also needed to test the underlying assumption that NTCP models that fit the photon data are applicable to protons. It does, however, pose challenges in terms of the required accuracy of the underlying models [81,82]. Secondly, development and validation of thresholds for NTCP reduction is critical for selection and can introduce tremendous heterogeneity in clinical trials [83].

Candidate patient populations for clinical trials

There are various clinical situations in which patients would benefit from proton therapy and where dose planning studies suggest a potential for improved outcome [84]. Advantages for proton radiotherapy are expected for thoracic tumors (e.g. NSCLC) and esophageal cancer with likewise low local control rates and a high risk for pulmonary or cardiac toxicity using standard radiotherapy regimens.

For brain tumors the potential reduction of neurocognitive impairment is a strong argument for choosing proton treatment. However, cost/benefit considerations and expected lifespan following treatment are relevant criteria for offering proton or photon radiotherapy. This qualifies rather lower grade gliomas than high risk glioblastoma multiforme (GBM) patients as candidates for proton treatment [62,85]. However, potential long-term survivors after GBM may profit from the better normal tissue sparing by proton radiotherapy, while patients with fast recurrences of a lower grade glioma may be equally well served with standard photon radiotherapy. While for low grade glioma stratification markers are emerging, for many cancer entities definite biomarkers are still lacking for predicting individual patient's treatment response. Head and neck squamous cell carcinoma (HNSCC) patients, for example, may profit from proton therapy due to reduced normal tissue toxicity and less late side effects. Especially the recurrent primary situation of HNSCC seem to be suitable for proton treatment while patients with good prognosis to standard treatment e.g. with human papilloma virus positive tumors, might be irradiated with photons [86]. The individually expected advantage of proton versus photon therapy is also dependent on the location of the tumor relative to the organs at risk, allowing prestratification of patients for HNSCC trials [87,88]. The reduced integral dose to the patient in proton treatment might allow for a dose escalation to increase local tumor control. Particularly in combined treatment regimens, the dose limiting factor of the normal tissue might be overcome with proton therapy. The most promising results from proton irradiation were achieved so far for pediatric patients. For this patient group, the reduction in secondary malignancies is important, but cannot be addressed as primary endpoint in prospective trials. National and international registries with lifelong follow-up of irradiated pediatric and young adults should be strongly supported by the radiotherapy community to generate a basis for long-term comparative studies in this area.

Future perspective and main research questions

Proton beam irradiation has not yet reached its full potential. A major underlying reason is the lack of detailed radiobiological knowledge particularly on the clinical distribution of radiobiological effectiveness and also on effects of combination with systemic chemo- or immunotherapies. Patient stratification based on biomarker expression is still missing to identify patients with highest probability to benefit from proton radiotherapy. Overall, among the most important research avenues for improvement of proton radiotherapy based on radiobiological knowledge are:

- Systematic preclinical experiments on RBE distribution as function of dose and LET in normal tissues of animals and/ or relevant three dimensional *in vitro* models using late toxicity endpoints or surrogate parameters of late toxicity.

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- Systematic preclinical evaluation of radiobiological (e.g. DNA repair, signal transduction, anti-vascular effects) and functional effects of chemotherapy or targeted drug combinations with protons versus photons including the development of biomarkers to predict tumor response.
- Development of biomarkers predicting late toxicity in patients. These can include tissue based markers but also imaging methods serving as surrogate markers. In the latter, voxel-based accuracy need to be improved. Image information need to be correlated with local dose and LET distributions. Image signatures, i.e. radiomics, may be a further strategy to predict treatment effects. Generally, biomarker development requires the collection of biomaterial, high-quality diagnostic images, and radiation treatment plans of all patients treated in prospective clinical trials.
- Translation of accumulating preclinical radiobiological knowledge into clinical proton radiotherapy treatment planning and stratification of patients for treatment in clinical trials.
- Reverse translation studies on RBE using large data bases integrating clinical outcome data, radiation treatment plans, initial and follow-up imaging studies, and (potential) biomarkers.
- Development of new clinical trial designs and involving patients and payers in how to make trials more attractive to stakeholders.
- Create large high-quality data repositories with detailed dosimetric and outcomes data for hypothesis-generating studies.

Overall, this list is not exhaustive. They should be taken as guiding research topics to further improve the quality of proton radiotherapy in patients. To efficiently address all items, a joint research strategy is required and co-operation among international centers providing equipment, personnel, and expertise to perform such research is needed.

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