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Review

Concepts and terms for dose/volume parameters in carbon-ion radiotherapy: Conclusions of the ULICE taskforce

Concepts et terminologie des paramètres de dose et volumes proposés en hadronthérapie par ions carbone

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ABSTRACT

Purpose. – The Union of Light Ion Centers in Europe (ULICE) program addressed the need for uniting scientific results for carbon-ion radiation therapy obtained by several institutions worldwide in different fields of excellence, and translating them into a real benefit to the community. Particularly, the concepts for dose/volume parameters developed in photon radiotherapy cannot be extrapolated to high linear energy transfer particles.
Methods and Materials. – The ULICE-WP2 taskforce included radiation oncologists involved in carbon-ion radiation therapy and International Commission on Radiation Units and Measurements, radiation biologists, expert physicists in the fields of carbon-ion radiation therapy, microdosimetry, biological modeling and image-guided radiotherapy. Consensual reports emerged from multiple discussions within both the restricted group and the wider ULICE community. Public deliverables were produced and disseminated to the European Commission.
Results. – Here we highlight the disparity in practices between treating centers, then address the main topics to finally elaborate specific recommendations. Although it appears relatively simple to add geometrical margins around the clinical target volume to obtain the planning target volume as performed in photon radiotherapy, this procedure is not appropriate for carbon-ion radiation therapy. Due to the variation of the radiation quality in depth, there is no generic relative biological effectiveness value for carbon-ions outside of an isolated point, for a given fractionation and specific experimental conditions. Absorbed dose and "equieffective dose" for specified conditions must always be reported.

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Conclusions. – This work contributed to the development of standard operating procedures for carbon-ion radiation therapy clinical trials. These procedures are now being applied, particularly in the first phase III international, multicenter trial (PHRC Étoile).

Mots clés :
Hadronthérapie
Ions carbone
Essai clinique
Indication
Dose isoefficace
Volume cible prévisionnel

RÉSUMÉ

Objectif de l'étude : Le programme *Union of Light Ion Centers in Europe* (ULICE) s'est proposé d'harmoniser et de favoriser la diffusion internationale des procédures et résultats de l'hadronthérapie par ions carbone. En particulier, les concepts pour les paramètres de volume et de dose recommandés en radiothérapie externe ou protonthérapie ne peuvent pas être extrapolés aux particules de transfert d'énergie linéique élevé.

Matériels et méthodes. – Le groupe de travail ULICE-WP2 comprenait des radiothérapeutes impliqués dans l'hadronthérapie par ions carbone et l'*International Commission on Radiation Units and Measurements* (ICRU), des biologistes, des physiciens experts en hadronthérapie, microdosimétrie, modélisation biologique et radiothérapie guidée par image. Des rapports consensuels ont émergé de discussions multiples, tant dans le groupe restreint que dans la communauté élargie d'ULICE. Les livrables publics ont été produits et diffusés auprès de la Commission européenne.

Résultats. – Nous avons mis en évidence une disparité des pratiques de prescription et spécification de la dose et des volumes entre les centres de traitement par ions carbone. Nous avons ensuite discuté des concepts fondamentaux qui s'appliquent à ces paramètres en hadronthérapie par ions carbone. Nous avons ensuite élaboré des recommandations spécifiques. Bien qu'il semble relativement simple d'ajouter des marges géométriques autour du volume cible anatomoclinique pour obtenir le volume cible prévisionnel en radiothérapie externe, cette procédure n'est pas appropriée pour l'hadronthérapie par ions carbone. En raison de la variation de la qualité du rayonnement en profondeur, il n'y a pas de valeur générique d'efficacité biologique relative pour les ions carbone en dehors d'un point isolé, pour un fractionnement donné et des conditions expérimentales spécifiques. La dose absorbée et la « dose isoefficace » pour des conditions spécifiées doivent toujours être signalées.

Conclusions. – Ce travail a contribué à l'élaboration de procédures standard pour la génération d'essais cliniques en l'hadronthérapie par ions carbone. Ces procédures sont désormais appliquées notamment dans le premier essai international multicentrique de phase III (programme hospitalier de recherche clinique Étoile).

1. Introduction

Advanced photon irradiation techniques offer a relevant but not yet fully optimized ballistic and/or radiobiological solution for 10 to 12% of human tumors characterized by their high-risk of local failure due to radio-unresponsiveness, hypoxia, or a critical location among sensitive healthy tissues [1,2]. Carbon-ions are densely ionizing particles with a high relative biological effectiveness, a lower oxygen enhancement ratio and higher level of physical selectivity compared to photons, justifying the use of hypofractionation [3,4].

Carbon-ion radiation therapy is available in very few centers worldwide. The first dedicated center for large-scale treatment opened in Japan in 1994, with five centers now active. Four European facilities are operational, two in Germany [Heidelberg (HIT) and Marburg (MIT)], Pavia (CNAO) in Italy, and Wiener-Neustadt (MedAustron) in Austria. Several carbon-ion radiation therapy projects are under consideration in the USA, following pioneering work at Berkeley [5]. Treating centers are equipped with two kinds of dose delivery systems, each of which has its own ballistic properties [6]. To date, more than 15,000 patients have been treated worldwide with carbon-ion radiation therapy, mainly in phase I and II trials [7–10].

Due to the high technical and financial investments required to expand carbon-ion radiation therapy practice, phase III studies comparing carbon-ions to protons or photons have been requested by the authorities but will be difficult to develop due to the rarity of eligible tumors and available centers [11,12]. Large-scale collaborations are required but are problematic for two historical reasons. Firstly, initial treatment facilities were established in academic and research environments, each developing their own technology and engineering. Secondly, various clinical research philosophies have been adopted; while Japanese centers have studied a broad spectrum of indications with dose escalation trials, hypo fractionated and passive beam shaping, the German facilities have treated small patient sets, developing fully active beam scanning, and a specific mapping of relative biological effectiveness-weighted dose. Consequently, prescribing, recording and reporting treatments differ significantly between centers, hampering comparability of treatments.

2. The ULICE project

The European CIRT scientific community has grown significantly over the last decade through multidisciplinary large-scale collaborations such as ENLIGHT [13]. The program entitled Union of Light Ion Centers in Europe (ULICE) was a 5-year framework program 7 capacities (FP7) project initiated in 2009 to address the need for greater access to carbon-ion radiation therapy facilities for particle therapy research (grant #228436). The program was established by 20 leading European research organizations, including the two existing European hadron research facilities, the European Society for Radiotherapy and Oncology (ESTRO) planned facilities, and two leading European industrial partners [14].

The WP2 aimed to develop joint concepts and terms for dose/volume and outcome assessment, standard operating procedures for clinical trial design, a clinical research infrastructure, and innovative tools. Specific topics were addressed in other work

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packages such as particle radiobiology (WP3), intrafractional moving targets (WP4), adaptive treatment planning (WP5), gantry engineering (WP6) or common database (WP7). The taskforce included radiation oncologists involved in carbon-ion radiation therapy and International Commission on Radiation Units and Measurements (ICRU), radiation biologists, expert physicists in the fields of carbon-ion radiation therapy, microdosimetry, biological modeling and image-guided radiotherapy. Consensual reports emerged from multiple discussions within both the restricted group and the wider ULICE community. Ten working parties were held with focus group or questionnaires submitted to the medical and scientific communities. Additional exchanges within the entire ULICE community occurred during the four annual meetings. The work package, pillar, and project coordinators validated deliverables before introduction to the European Commission.

3. Concepts and terms for dose/volume parameters: state of the art, technologies and practices

3.1. Planning target volume

The planning target volume (PTV) is a geometrical concept introduced for treatment planning, dose prescription, dose volume reporting and evaluation. In ICRU report 62, it was recommended that for external beam photon radiotherapy, internal and set-up margins be added quadratically [7]. The concept of PTV is particularly complex in regard to carbon-ion radiation therapy and this procedure appears inadequate due to the physical properties of the particles and the resulting higher heterogeneity of dose distribution.

In addition to the typical geometric uncertainties, PTV delineation requires additional depth margins to take into account range uncertainties. When using a single beam, they could theoretically be added resulting in a combined anisotropic shell around the clinical target volume (CTV). However when two (or more) non-parallel opposed particle beams are applied, delineation of a (unique) PTV would raise complex computation issues for the treatment planning system (TPS) [15].

Active beam delivery techniques raise additional issues. X-ray, electron and passively scattered charged particles beams have a physical continuity and homogeneity of the irradiated volume at any time so that only the margins and distance are influenced by the uncertainties of position, but not the internal homogeneity of dose deposition. On the contrary, the charged particles beams produced by active control techniques (beam scanning, raster scanning, spot scanning) are inherently heterogeneous in time and space. The dose is not prescribed to a reference point but to each voxel. Moreover, organ motion and tissue heterogeneities may have a strong impact on dose distribution such as interplay effects [16,17]. Interplay effects arise because both the beam delivery and the target of that delivery are changing with time. Two issues are thus crucial in this area:

- first, the techniques of motion compensation (repainting, tracking, etc.), which are very sophisticated but with promising results;
- second, the techniques of quality control which are neither available yet nor having an expected level of precision able to ensure, a real-time or deferred time, quality of dose deposition in tissues (and not only the quality of the particle distribution in space). Indeed, a dose heterogeneity of a millimeter scale and several percent is not yet measurable, by far.

Specific attention and complex irradiation techniques are needed to alleviate the motion effect in carbon-ion radiation therapy [18–20].

3.2. Biological dose, linear energy transfer and relative biological effectiveness

The ICRU thus recommends that the absorbed dose distribution (3D) and the associated temporal data are systematically reported accurately and completely, to allow interpretation of the effects and to reconstruct the irradiation conditions if needed [21,22]. However, specification of this quantity alone is not usually sufficient to predict biological effects when comparing treatments in different patients and/or under different irradiation conditions, including radiation quality.

Radiation quality – specified using linear energy transfer – is defined by the type, energy and directional spectra of the ionizing particles at the point of interest. In carbon-ion radiation therapy, contrarily to low linear energy transfer radiotherapy, the particle energy spectrum greatly varies along the ion path within the treated volume. Each voxel receives a mixed field of particles due to fragmentation, so the same physical dose at a given point may correspond to different particle spectra, each of which could lead to a particular biological and clinical effect [23].

The concept of relative biological effectiveness was jointly introduced by the International Commission on Radiological Protection (ICRP) and the ICRU to compare the biological effects of different radiation qualities [24]. A relative biological effectiveness value is meaningful only to the extent that the reference radiation quality, the biological system, effect, absorbed dose and irradiation conditions are specified, and is thus only valid for the conditions under which it was determined. Absorbed doses are never totally homogeneous and the relative biological effectiveness (dose ratios) can only be determined accurately at reference points and/or in defined volumes.

In conventional photon radiotherapy, outcomes are related to the dose, with little dependence on beam energy but a strong dependence on dose per fraction, in contrast to high linear energy transfer radiotherapy – that minimizes the involvement of relative biological effectiveness in the biological dose, making a true comparison with current fractionated treatments very difficult.

3.3. ICRU and International Atomic Energy Agency (IAEA) recommendations

Propositions have been made to extrapolate dose/volume parameters from the ICRU recommendations for conformal and intensity modulated photon radiotherapy [7,21]. The major difference lies in the use of dose/volume reporting and the amount of technical data required for proton therapy.

According to ICRU report 78, as a proton-beam requires different margins (lateral and depth), a different PTV must be used for each possible beam direction and for dose reporting. An adjustment is advised within the beam design algorithm to account for differences between these two types of margins. Formulas relating magnitude of errors to a unique PTV margin should be avoided.

Reporting the absorbed dose alone appears insufficient. Recommendations in the report include the use of a generic relative biological effectiveness value of 1.1 and the concept of a relative biological effectiveness-weighted absorbed dose (DRBE, the product of the proton absorbed dose [D] and proton relative biological effectiveness). However concerns have been raised about the insufficiently protective effect of this generic relative biological effectiveness, notably for the nervous system [25].

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Experts from the ICRU and IAEA discussed the fundamental issues that must be resolved to reach an agreement for reporting. No official operational recommendations emerged [26].

3.4. Practices of treating centers

At the NIRS (Chiba, Japan), which has been treating patients since 1994, a minimum isotropic margin is assigned for the "global" PTV to account for setup uncertainty, which is usually smaller than the range uncertainty. Therefore, the excess of the range uncertainty is usually considered by additional depth margin to cover the PTV with the spread-out Bragg-peak of each beam. A stationary delivery and margins-based approach – such as the use of an internal target volume (ITV) – is usually performed for tumors with slight movement, including with an adequate immobilization. Internal target volume (ITV) consists of an internal margin added to the CTV to compensate for internal physiologic movement and variations in size, shape, and position of the CTV. For tumors with greater movement (lung and liver), techniques that reduce motion amplitude are used (gating, adapted margins by performing multiple CT scans, rescanning/repainting, tracking). Human salivary gland tumor cells were used for relative biological effectiveness calibration [27]. Since 2012, the NIRS can treat patients with either passive scattering or 3D raster scanning and is using a modified microdosimetric kinetic model for relative biological effectiveness calculation [28].

In Germany, the PTV is usually obtained by adding an isotropic margin from the CTV, whose absolute value varies by body region. Active scanning has been used since 1997 to treat static tumors. The PTV is decomposed into voxels – each being actively and sequentially irradiated with different radiation qualities due to the modulation of the native pencil beam. Conformal dose distributions can be achieved by optimizing the number and incidence of the beams. Relative biological effectiveness is calculated for each voxel according to the local effect model [29].

There is no current agreement on the biological and biophysical hypotheses sustaining the three models used to predict relative biological effectiveness in the operating facilities.

This raises the issue of comparability between treatments and the need to implement international clinical trials [30]. Fortuitously, clinical outcomes from Germany are nonetheless comparable to those obtained in Japan [31].

Harmonization of definition of concepts and terms, volumes, dosimetric and radiobiological protocols, methods for reporting dose and evaluation of outcome is essential for relevant compilation and exchange of data and for deriving definitive conclusions concerning the medical merit of carbon-ion radiation therapy. The present paper provides specific recommendations in the framework of the ULICE working package 2.1.

4. Recommendations

In the absence of specific recommendations from the ICRU, we propose here consensual, and when necessary, original concepts to better define and understand the biological dose and its determinants. We address three main areas: (1) quantities and units, (2) volume concepts, and (3) recommendations for reporting.

4.1. Equieffective dose concept and units

In the context of exchanging clinical information, comparing or combining treatments performed under different technical conditions required the introduction of a bioeffective dose concept. Relative biological effectiveness, which requires equivalent conditions in compared irradiation modalities, is a fundamentally different quantity [32]. The concept of "equieffective absorbed dose" was introduced by the IAEA and the ICRU for radiation therapy applications [26]. The equieffective dose, EQD, is defined as the product of the absorbed dose (D) and a weighting factor, W_{EQD} that takes into account the effects of all parameters that could influence the outcome (Fig. 1).

A given value of EQD (or W_{EQD}) is meaningful only to the extent that the following conditions are fulfilled:

- the reference irradiation conditions are specified (fractionation, overall time, radiation quality);

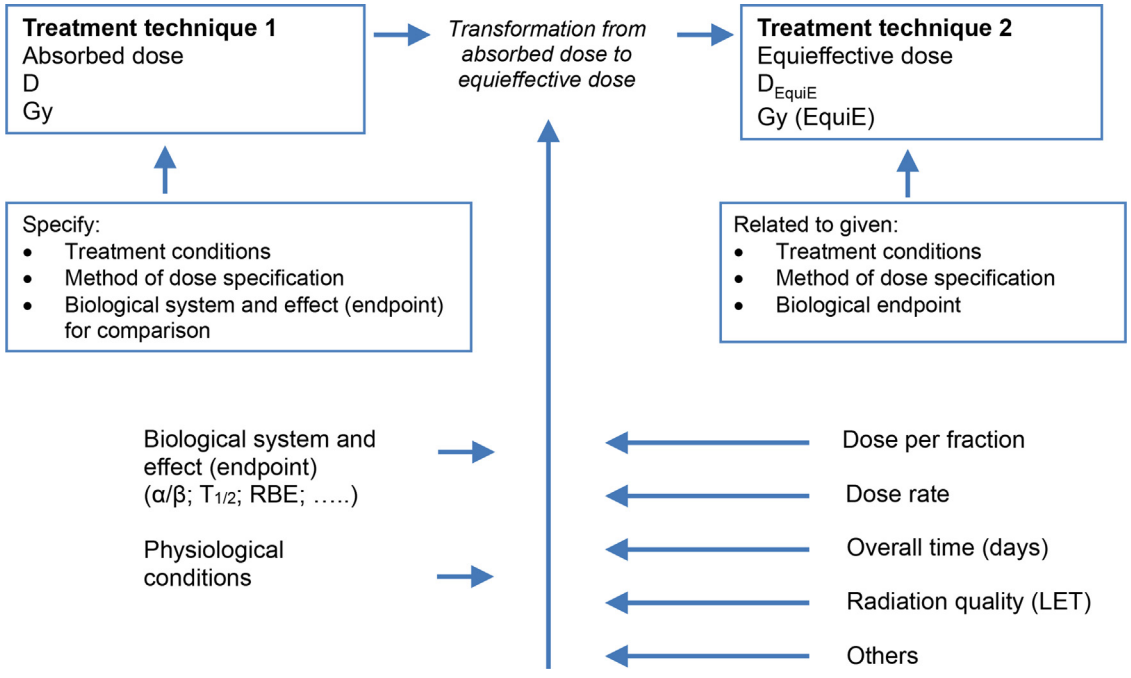

Fig. 1. Comparison of different radiation treatment techniques: transformation function of absorbed dose, D, to equieffective dose, EQD, applicable to all types of techniques.

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- the biological systems and effects for which EQD and W_{EQD} have been selected is specified;
- the tissue volume selected for evaluation of the equieffective dose is specified;
- the method used to specify the prescribed/delivered dose to the PTV is indicated (dose–volume histograms curve and/or selected relevant points) and should be the same for the compared treatment modalities;
- the biological model used is valid for the dose and fractionation schedule evaluated.

To avoid confusion between "Gy" used as the symbol for the (physical) quantity absorbed dose (D) and the quantity equieffective dose (EQD), it is current practice to use the symbol "Gy EQD" when the symbol refers to the biologically transformed quantity equieffective dose (EQD). While this is generally applied in clinical practice, it is not in agreement with the international system [33].

4.2. Volume concepts and margins applicable to carbon-ion radiation therapy

As general recommendations, we state that:

- for particle therapy a geometrical PTV is not adequate;
- formulas relating magnitude of errors to PTV margins should not be employed;
- PTV should account for the major changes in dose distribution shape that may result from deviations between treatment and planned conditions;
- if we consider that the PTV is only defined by the addition to the CTV of all the positional and anatomic uncertainties (motion, shape, tissues composition, repositioning and set-up, etc) one could consider in principle a unique PTV for each CTV. When designing the treatment and choosing the beams, additional uncertainties related to tissue characteristics, beam and radiation qualities will appear and determine the parameters to compute in the treatment plan that is transferred to the accelerator. Each beam will need a specific treatment plan to contribute to the irradiation according to the prescription. However, there is presently no way to prescribe a simultaneously optimized multiportal particle treatment with portal specific PTV;
- new algorithms with uncertainty-oriented optimization should be investigated for active scanning delivery; until then, a single PTV should be delineated but resulting plans should be checked for robustness against deviations between planned and actual treatment conditions.

Every effort should be made to realistically assess, either with repeated imaging or with software processing of image data, the real effect of deviations from planned versus actual treatment conditions. When it is not possible to measure such deviations, the PTV delineation should be a medical act that takes into account all aforementioned issues [34].

4.3. Recommendations for carbon-ion radiation therapy prescription and reporting

4.3.1. Volumes

When reporting treatments, it is essential to specify the volumes on which the doses are delivered. When carbon-ion radiation therapy is part of a combined cancer therapy strategy (e.g., a boost), the volumes reported for ion-beam therapy should correspond to the time when carbon-ion radiation therapy is started. When different techniques are combined in the global treatment strategy, different PTV may be defined. Doses cannot be compared/combined/added if they are not related to common geographical reference points or coordinate systems.

In addition to the common parameters recommended in level 3 situations defined in ICRU report 62 [7] such as proton radiotherapy (ICRU report 78 [15]), the following parameters influencing the shape of the PTV should be reported: type of accelerator, treatment-delivery equipment, beam-delivery technique, beam-shaping configuration(s) including patient and field-specific hardware such as collimators and compensators or the details of the scanning system and pencil-beam parameters; One PTV specific for each beam should be employed in passive scattering delivery. The report should include the specification of the corresponding CTV (and GTV and/or BTV sustained by functional imaging if relevant) [34]. The margins in depth and lateral must be documented.

4.3.2. Introduction of 4D-CT

More recently, variation of dose distribution as a function of time has been investigated in terms of 4D-dose distribution (ULICE WP5 reports). CTV may be imaged using several free breathing conditions. A global treatment plan can be calculated for each condition [35]. Summation of all the plans into a single simulation CT data set will result in a treated volume larger than the CTV. In this situation, a cumulative dose/volume histogram may be reported on a static reference slice (mid-position?), thus overestimating the dose deposited laterally. Advanced concepts of dose/volume histogram may address this in the future, notably dose-mass histograms rather than dose/volume histograms, and probabilistic dose/volume histogram with a CTV–dose/volume histogram confidence interval [36].

4.3.3. Absorbed and bioeffective dose

From currently available data it can be concluded that, in contrast to protons, a single (generic) relative biological effectiveness value cannot be recommended for carbon-ions. In the absence of modeling of an equieffective dose, we propose reporting the absorbed dose distribution (3D) and associated time parameters such as average and instantaneous dose rates, particle fluence, overall time [37], and to save the primary data for each beam with all the physical characteristics of each individual particle, based on the calculation of the range and linear energy transfer. Current technology allows linear energy transfer spectra to be computed at selected points and volumes. In addition (not instead of), the relevant equieffective dose must be reported.

If the approach and methods used to perform dose transformation and to evaluate EQD are fully specified, evaluation of these quantities can be repeated using different hypotheses or models.

All factors involved in the transformation function of the absorbed dose into the bioeffective dose should be specified as well as the quality, energy, and coordinates of every particle to support further bioeffective dose modeling [38].

4.3.4. Reporting dose/volume histogram and dose

The dose/volume histogram should be reported for all volumes and both quantities (i.e., absorbed dose and equieffective dose under the conditions highlighted above). For the tumor-related dose/volume histogram, D50, D98 and D02 values must be reported to facilitate exchange of information between centers. In addition, other dose levels can be reported if useful.

When different techniques are combined in the global treatment strategy, different PTV may be defined. Adding the corresponding doses may be difficult and selection of the traditional ICRU reference point specified relative to well-defined anatomical reference has obvious advantages. The concept underlying the selection of this reference point and its limitation in particular cases has been discussed previously [7].

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When passive scattering is used, it is straightforward to specify both doses to the PTV at a point on the beam axes at the center of the spread-out Bragg-peak (selected as the ICRU reference point), not at the proximal peak of the spread-out Bragg-peak where the dose can change dramatically. In contrast, the choice of selected doses on the dose/volume histogram is more appropriate when using scanning beam. The method used to specify the PTV dose must be the same for the reference and the treatment modality used.

Computing and displaying the dose distributions in the appropriate planes allows selection of the most relevant reference points for reporting and comparison of the outcomes, avoiding pitfalls related to dose heterogeneity. Reporting only the dose/volume histogram lacks an anatomical reference, which is important when different treatment modalities are combined or compared.

As for dose/volume histograms, absorbed doses and equieffective doses must be reported at the selected reference point(s) [37].

4.4. Ensuring dosimetric intercomparison between facilities

The features of scanning beam delivery complicate dosimetric intercomparison between facilities and require specific procedure. The most efficient solution is a so-called end-to-end test auditing procedure [39]. The purpose is not just to validate beam line monitor calibration but also to confirm that the entire logic chain of radiation treatment is operable and will give the desired results with sufficient accuracy. Such tests are designed based on the use of a plastic phantom that hosts a set of alanine detectors and radiochromic films distributed over the predefined target volume [40]. If multiple institutions are planning to participate in clinical trials, external auditing dosimetry studies are mandatory and the proposed test may serve as an accreditation procedure [41].

5. Future directions

5.1. The PTV issue

In the present state of knowledge and techniques, established concepts are well suited to treat immobile or immobilized tumours in a stationary environment.

The effects of different beam arrangements on the target expansions necessary to ensure a predefined level of plan robustness have recently been investigated. A non-isotropical expansion rule based on the concept of weighted margins according to the probability of the presence of the target has been proposed [42]. Irrespective of the residual movements, and whether or not they can be modeled, available tools for quality control of the dose distribution do not guarantee an absence of overdosing or, more importantly, of underdosing in the CTV.

To address the issue of organ motion, the goal of ULICE WP 4.2 was the development of a monitoring system, which most likely comprises motion models that can be used to track the tumor in the carbon-ion radiation therapy centers [43]. WP 4.3 produced a prototype implemented at CNAO, Pavia, Italy [44]. As an alternative to tracking, HIT, Heidelberg, Germany explores rescanning [45]. In principle, rescanning is less favorable than tracking because the normal tissue burden is increased but since its robustness to changes in e.g. breathing pattern is much better compared to tracking an early clinical use that would be beneficial for a subset of patients is likely.

5.2. Alternative models predicting relative biological effectiveness

Besides the three radiobiological models described above, other models could also be applied to carbon-ion radiation therapy. Alternative models are under development, or are being actively researched in the domain of nano- and microdosimetry [46]. A model-independent interface for relative biological effectiveness predictions is being implemented [47].

Trying to reach a consensus too soon is likely to lead to a non-scientific choice and a failed solution. It is urgent to convince companies developing treatment planning systems to modify their software, on the one hand to store and provide access to sufficient information on treatment plans for rigorous research programs and on the other to exploit relevant biophysics models.

5.3. The relative biological effectiveness issue

Since fractionation regimens differ from 3D-CRT, α/β ratios for dose-limiting toxicity and the specific tumor cell type are expected to differ substantially [48]. Radiobiological data for both human tumors and healthy tissues are lacking. Ideally, prospective experiments should be performed, with specific attention to the linear energy transfer–bioeffective dose turnover point position for different ions, the initial slope of the increment in relative biological effectiveness, and the maximum α and β values relative to their low linear energy transfer values. A dedicated and coordinated European radiobiological program is planned [49].

5.4. Bioeffective dose

Future studies should address the different modalities of dose weighting with ballistic and biological dimensions and to define probability thresholds to associate with the dose prescription. Noteworthy, some of these factors – such as the radiobiological effects of the radiation qualities from a single beam, microdosimetric data, the use of chemotherapy or biological response modifiers – are not even precisely known for photon beams.

6. Conclusions

Through international cooperation, the carbon-ion radiation therapy community needs to coordinate therapy planning and delivery in such a way that clinical results can be collected in the framework of multicenter prospective trials. Efforts must be made to develop procedures, which will produce readily comparable results, with reliable and verifiable dosimetry reporting. ULICE's commitment was primarily to transnational exchanges and multilateral access to promote such collaboration. In this respect, dose and volume specifications for prescribing and reporting ion-beam therapy are critical points, and the ICRU report on these topics should detail and emphasize global recommendation for particle therapy. Until then, current facilities should operate according to these recommendations, to facilitate and optimize clinical research.

In contrast to protons, a single (generic) relative biological effectiveness value cannot be recommended for carbon-ions. In the absence of modeling of an equieffective dose, we propose reporting the absorbed dose distribution (3D) and associated time parameters such as average and instantaneous dose rates, particle fluence, overall time, and to store the primary data for each beam with all the physical characteristics of each individual particle, based on the calculation of the range and linear energy transfer.

The concept of PTV is particularly complex, if not applicable, in regard to particle therapy treatments. Currently, concepts for specifying volumes in carbon-ion radiation therapy are those of conventional radiotherapy and protontherapy as defined by the ICRU.

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We recommended to report separately the PTV for each beam and it would be preferable to specify different "vectors" of the PTV construct: technical factors mainly related to the beam-shaping technique on the one hand, and patient-related factors linked with tissue heterogeneities and motion on the other hand.

Established concepts are well suited to treat immobile or immobilized tumours in a stationary environment. Tumor or organs at risk motion is certainly the most limiting issue for the implementation of active beam techniques. This underscores the relevance of particle beam therapy techniques that would be less sensitive to the movements of the target to enlarge the scope of therapeutic indications. Whatever the techniques used to address motion, this topic remains in the domain of research and development.

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Disclosure of interest

The authors declare that they have no competing interest.

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