Minimum and optimal requirements for a safe clinical implementation of ultra-high dose rate radiotherapy: a focus on patient's safety and radiation protection

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1. Introduction

Studies in multiple animal species have shown that ultra-high dose rate (UHDR) irradiations improve normal tissue sparing while providing equivalent tumor control compared to conventional dose rates. This effect is called the 'FLASH' effect.

After a number of favorable pre-clinical experiments and the first patients treated, clinical trials have been launched [1-7] and the clinical transfer of UHDR radiation therapy (UHDR-RT) will probably occur in the next few years. The clinical implementation of UHDR-RT needs to be performed with the highest level of safety to prevent adverse events.

Multiple UHDR-RT modalities have been proposed including high-energy electrons (HEE, 4-50 MeV) [8-10], very high-energy electrons (VHEE, 50-300 MeV) [11, 12], MV photons [13] ,proton [6, 14-16] and ion beams [17]. HEE and proton beams are closest to clinical transfer because existing (pre)clinical devices are already capable to reach UHDR conditions, and UHDR VHEE machines will most likely be clinically implemented in the next 5 years. Therefore, in the following discussion we will mainly focus on HEE, VHEE and proton beams. However, many of our recommendations could be extended to other beam types, and we will indicate such possibilities in the text. Taylor et al. [18] designed a roadmap to safe and effective clinical trials of FLASH RT highlighting the technological and process requirements with respect to conventional RT to enable the clinical translation. Several recommendations have been made, and among these one suggested that international organizations such as AAPM, ESTRO and EFOMP continue to collaborate on guidance. More recently, Zou et al. [19] proposed a framework on quality assurance (QA) on UHDR-RT clinical trials and reviewed current technology gaps to overcome, with a focus on electron and proton modalities.

The main objective of this document is to highlight specific requirements that the radiation oncology community should need to address to harmonize and standardize important aspects of UHDR-RT related to patient safety and radiation protection. In particular, because UHDR-RT is still in its infancy, two levels of requirements have been defined: a) minimum requirements related to the state of the art for safe clinical implementation and b) optimal requirements to be fulfilled when specific technology becomes available in the future. As much as possible, these requirements have been extended from and are in line with existing guidelines for conventional RT delivery techniques [20-25], which represent the standard-of-care references for any novel UHDR

delivery technique. For VHEE RT and other newly emerging UHDR treatment modalities for which no respective established conventional technique and recommendations exist, one or a mixture of multiple recommendations could be followed, as applicable. For instance, established recommendations for intensity-modulated radiotherapy, electron and proton RT may be relevant for VHEE RT using scanned beams. Therefore, inter-comparability based on conventionally established criteria should be ensured.

The FLASH effect has been observed in experiments starting from dose rates around 30 Gy/s and irradiation times below 1 s. Therefore, these recommendations can be considered to be valid starting from around this dose rate. However, the exact threshold in beam current for UHDR might be different depending on the delivery technique and/or the machine considered, and therefore particular care needs to be taken when implementing these recommendations, especially for dose rate levels close to this threshold.

Another objective is to steer a revision of RT regulations that takes into consideration the specific needs of UHDR-RT.

It is not the intent of this work to provide information about machine commissioning or technical and dosimetric challenges of UHDR-RT. These topics are or will be covered by publications coming from working groups, such as the UHDPulse project group [26] , AAPM/ESTRO task group 359 [27], and the recently established ESTRO FLASH Focus Group.

This paper and another one in preparation on recording and reporting of UHDR-RT originated from the ESTRO physics workshop on “Physics aspects of FLASH”, held in October 2021.

This work is structured in three sections. The first section addresses patient and staff safety issues related to the use of UHDR beams, such as beam monitoring and the requirements for radiation protection. The second section deals with patient safety in the simulation, treatment delivery, and verification phases, and the last section is dedicated to QA.

2. Safety, radiation protection and regulation

Radiation exposure at RT doses is always linked to a significant health risk, and therefore dedicated practices for mitigating these risks for patients and personnel are required. International guidelines and recommendations have been established for safety and radiation

protection rules in conventional RT [28-32] and most countries have developed their own regulatory bodies based on these international guidelines and recommendations.

The International Electrotechnical Commission defines the main international standards for the medical devices used in RT (electron/ photon [24], and proton/ion beam [25] machines. Many of the recommendations provided in these standards apply to both conventional and UHDR irradiations, for instance monitoring of the absorbed dose, and using independent and redundant dose monitoring systems. However, other recommendations, such as the use of on-line displays of spot positions or beam flatness, are not achievable for the sub-second deliveries used in UHDR-RT. These crucial timing and dose rate requirements demand novel concepts and innovative devices for beam monitoring. In addition to the QA programs, prescribed for conventional RT, the development and use of on-line monitoring, verification, and timely automated out-of-tolerance delivery interruptions are more important than ever with the emergence of UHDR-RT, since human detection of a delivery error would be impossible before the end of the treatment.

Moreover, future UHDR treatment guidelines will need to be integrated with dose rate considerations if the dose rate is used to achieve better sparing of healthy tissues. A sudden drop of dose rate may affect the expected FLASH effect unless it is mitigated during the treatment. Nevertheless, current biological knowledge does not allow for a precise determination of how treatment interruptions should be managed. Clinical protocols should consider how a UHDR treatment could be completed if a fraction is interrupted because of an error in delivery. For instance, by compensating missing dose during the next UHDR fractions or by converting the treatments to a CONV treatment for remaining the fractions.

The beam parameters that trigger the FLASH effect are not yet precisely characterized and mechanistically understood, which mandates additional caution [33-37]. Thus, better understanding of the radiobiological mechanism of the FLASH effect, standardized terminology, and recording and reporting guidelines for UHDR-specific parameters are needed. Guidelines on “Recording and Reporting” originated from the same ESTRO Physics workshop on “Physics aspects of flash” and are in preparation.

Beam monitoring

The clinical translation of UHDR-RT poses several challenges and requirements that cannot be met by existing monitoring systems used in conventional dose rate beams. In conventional photon, electron and proton/ion RT, monitoring ionization chambers (or monitor chambers) are the most commonly used devices to control the dose output of the beam. These monitor chambers, typically arranged in segments or strips, also allow monitoring of the output, flatness, and symmetry of the beam [38, 39]. However, such monitoring devices suffer from large recombination effects at the dose rates associated with UHDR irradiations [40-42] and from limited speed of operation, which poses a significant metrological challenge for their application in UDHR beams. An UHDR beam monitoring system should ideally also have the capability for real-time monitoring (i.e. monitoring the temporal structure of the beam), including instantaneous monitoring of dose rate, pulse duration, pulse repetition rate, and the dose rate per delivered spot in scanning beam systems [43, 44]. Currently such solution does not exist. However, we envisage that, as the field moves forward, new instruments, including hybrid devices incorporating capabilities of beam current transformers (BCTs), ionization chambers and solid-state detectors, will become available. An overview of the devices under investigation for UHDR beam monitoring can be found in Romano et. al [45] and in Subiel and Romano [46]. Since the FLASH effect has been observed in various beams with different temporal beam structures, each with their own challenges and monitoring requirements, we will describe these for each type of delivery system individually.

For UHDR HEE RT [40, 47-49], BCTs are currently the most prominent devices to monitor the beam fluence. These have been shown to have a linear charge-dose relationship, independent of pulse width, with standard uncertainty below 3% in UHDR, and to guarantee good short- and long-term stability [50-52]. In addition, BCTs are non-destructive, fast, and do not interfere with the beam [52, 53]. However, they cannot monitor spatial beam properties such as flatness, symmetry and beam size.

For UHDR proton, ion, and VHEE RT [8, 14, 17, 54], scanning and collimated broad beam (scattering) techniques can be distinguished. The parameters of main interest for scanning beams are beam dose output per spot, transverse position, and energy for each pencil beam scanning (PBS) beam. For scattered beams, the beam dose output, field size, and characteristics such as

flatness, and energy should be monitored. Additionally, and specifically in relation to UHDR, the irradiation time and delivery sequence should be monitored for PBS beams. Most facilities have long beamlines, and any beam fluctuation could affect the dose rate administered at the patient location. For future UHDR irradiations, it is likely that dynamic energy modulation cannot be used, since even the fastest systems need tens of milliseconds to change the energy. It is more probable that a single-energy beam will reach the treatment room, with more energy modulation performed at the beam exit using compensators or ridge/ripple filters [55-57]. Therefore, monitoring the energy will not require additional adaptations of methods commonly used in clinics [58]. Concerning transverse dimensions, clinics usually monitor spot position and field size/center, when employing PBS and scattering techniques, respectively. Spot size clinical tolerances are relatively relaxed, because the spot size variation doesn't have a huge impact in the final dose distribution, definitely much less than spot position variation. On the other hand, spot size variations might be more important for PBS when evaluating dose rate maps, particularly if undegraded beams are used, as high energy beams scatter less and may be more affected by the daily accelerator conditions. Nevertheless, whether this would be more important than position variations, and which tolerance level should be set is very hard to say based on current evidence.

The recombination effect observed at UHDR for current ionization-based monitoring solutions (multi-wire proportional chambers, strip, or pixel detectors) can still be corrected for at dose rates currently available with clinical proton accelerators (such asynchronous cyclotrons), but may be more challenging for synchrocyclotrons.

Recombination depends on the charge density, and therefore ionization-based measurements become problematic with very high charge densities, such as in laser-driven accelerators [59-61]; in these cases, integrated current transformers have been proposed to monitor beam fluence [60]."

For PBS, real-time beam size monitoring could potentially be implemented on segmented detectors, already used in clinic for spot position monitoring ; However, since recombination depends on charge density (and therefore also on the beam size), algorithms to reconstruct beam size at UHDR might require longer signal processing time (as information such as the beam current, for example, might be required for a correction). Moreover, it is hard to suggest a tolerance on beam size for UHDR monitoring purposes, as this will likely be machine dependent,

and potentially also depend on the definition of the FLASH effect for PBS. Therefore, it should be considered as an optimal requirement. If the beam size is not measured in real-time, its stability should be validated and monitored. This could be achieved, for example, by increasing the QA frequency with respect to what is commonly done for clinical PBS. As long as interrupting an individual pulse is not possible due to temporal restrictions, we would also recommend the use of beam-monitoring devices to adapt the next pulse to compensate for deviations of previously delivered pulses, if allowed by the speed of operation of the system. Such a technology represents an optimal requirement for safe patient treatment in UHDR beams in the future. This concept is in principle applicable to all pulse-based UHDR modalities; however, a feedback mechanism can only work optimally if the dose is delivered in more than one pulse. It is under development for electron beams, and a similar feedback correction is implemented in proton synchrocyclotrons. Notably, the implementation in proton synchrocyclotrons foresees that each spot is delivered in more than one pulse, so that a feedback correction is always possible; moreover, the last pulse is always relatively small, so that even an error in the last pulse will not strongly affect the delivery of the spot. For (pseudo-)continuous beams, alternative correction mechanisms need to be considered.

In summary, beam monitoring for UHDR irradiations is a field of development. The minimum and optimal levels of requirements are proposed in table 1.

Until a real-time[1], 2D monitoring device, and eventually solutions for real-time dose adaption (or beam interruption) that are fed by this monitoring device, become available, a pragmatic approach can be used to determine the minimal requirements for safe clinical implementation. Specifically, for the first clinical implementations of UHDR beams, a viable approach might be to verify, both before and after each treatment, that all parameters (e.g. beam flatness, symmetry and energy)[40, 51, 62, 63] are within tolerances, provided that the system exhibits very good long- and short-term stability in relation to these parameters. As this approach would ensure the best practice possible to date, its use is advisable for initial clinical implementations in carefully monitored clinical trials.

[1] Real-time device = a device that functions within a time frame comparable to the temporal resolution of UHDR-RT (e.g. the real-time reading frequency should be sufficient to ensure a dose reading accuracy better than 3% of the dose per pulse/fraction for broad collimated beams or 3% of the dose per spot for scanning beams).

In case deviations occur, actions will be specific to the treatment protocol, the patient case, the site of occurrence, as well as the magnitude and direction of deviation. While basic scenarios (under-dosage, over-dosage, dropping of dose rate) need to be considered when establishing a clinical UHDR treatment protocol, in case of occurrence, the individual dosimetry and patient case need to be carefully evaluated by an expert team involving radiation oncologist(s) and medical physicist(s) to take the most suitable actions. For instance, in case of under-dosage, missing dose might be compensated by a future UHDR fraction or the treatment might be converted to a CONV treatment for remaining fractions.

Radiation protection and regulation

The thickness of the required shielding for external beam therapy is usually calculated based on considerations such as the dose limits outside the shielding barriers, the beam type, its energy spectrum, its directions and the presence of leakage and scattered radiation, as reported in IAEA Safety Report Series 38 [28]. Different countries define different dose limits for occupational exposure or the public, using different quantities such as instantaneous dose rate, dose in-any-hour, weekly dose, or time-averaged dose rate (after accounting for occupancy and workload). As the prescribed absorbed doses and fractionation schedules of UHDR treatments are not expected to differ substantially from current hypofractionation regimen and stereotactic body RT (SBRT) dose ranges and schedules, in radiation oncology departments, and assuming that the number of patients treated per hour will be less than or equal to current practice, we recommend that national regulations be adapted to include UHDR irradiation so that instantaneous dose rate (or short time-averaged dose rate) do not artificially limit the use of UHDR beams. In other words, careful monitoring of the delivered dose (e.g. with BCTs, particularly suited for UHDR HEE) with clear limits based on daily or weekly workload (as recommended in NCRP 151 report [29]) should be established in order to protect staff and the public.

In addition, reassessment of the shielding might be needed in special cases, for example for UHDR proton therapy in transmission mode (in contrast with the standard clinical mode of operation, where the beam stops in the patient), in case accessories are used with conformal UHDR-RT, or for linear accelerator vaults converted from photon therapy to UHDR electron

therapy [64]. In such cases, a survey of the photon and neutron radiation outside the barriers should be performed, ensuring that only detectors appropriate for pulsed irradiations are used [65].

For commissioning or QA procedures that significantly increase the workload with respect to clinical practice, ad-hoc procedures should be established (e.g., in separate rooms with specific derogations allowed by the competent authorities). The machine tests that do not require testing in the UHDR mode such as door interlocks and mechanical motions can be performed in CONV mode to reduce workload [10].

Particularly for the introduction of a new technology, harmonization in safety and radiation protection regulations between different countries would be desirable. Moreover, such alignment between safety practices in different countries will pave the way for a better harmonization of protocols for the applications of UHDR-RT to human patients.

3. Simulation, in-room image guidance and treatment delivery verification

Imaging in UHDR-RT may become a non-trivial factor in effective treatment planning and safe treatment delivery. UHDR pulsed beams inspire new approaches and developments in imaging, because they increase the signal-to-noise ratio of imaging modalities such as ultrasound (thermoacoustic signals) [66] and Cherenkov emission [67], making these imaging modalities good candidates for on-line treatment verification in UHDR-RT. We refer the reader to El Naqa et al. for an overview of technical solutions and requirements for UHDR-RT image guidance [68]. However, it should be noted that smooth clinical implementation of these new imaging modalities would require the adaptation of testing protocols and new quality control procedures. Below we briefly present the most important, feasible, and efficient requirements regarding imaging in the RT chain, according to their current availability in clinics.

Simulation

Patient immobilization and simulation procedures should follow the same guidelines used for conventional SBRT, image-guided RT, and motion mitigation in particle therapy [69-74].

In-room image guidance

Except for specific cases (i.e., superficial tumors), in-room imaging should be required before each treatment delivery using state-of-the-art imaging devices and techniques to ensure patient safety and the accuracy of treatment delivery [75]. Imaging with higher temporal resolution compared to conventional RT is required to guarantee that the extremely short UHDR treatment is delivered precisely.

Physiological motion is 'frozen' with respect to the timescales of UHDR-RT; therefore, the main concern of motion monitoring is assessing the reproducibility of free breathing (avoiding any baseline drift or sudden modification of the amplitude of the breathing) or of the pre-defined level of breath-hold, either for an UHDR irradiation in a single fraction or multiple fractions. Four-dimensional cone-beam CT could be useful to assess the reproducibility of the tumor motion evaluated in the 4D-CT simulation. It will be even more important (compared to conventional RT) to ensure that there is no involuntary or sudden patient motion (e.g. sneezing/coughing) during the sub-second delivery time. Therefore, the patient should be well instructed to avoid such sudden movements. Beam-on triggering, based on tumor motion tracking in a pre-defined phase of the breathing cycle (including breath-hold) or on modelling of the tumor motion compared to external movement, would be desirable. These considerations hold also for PBS-FLASH: even though it is not yet clear how large volumes could be irradiated with PBS-FLASH, at least for small volumes we can expect the deadtimes between different spots to not dramatically lengthen the irradiation time. Therefore, also for PBS-FLASH we can expect the irradiation to last much less than a breathing cycle, and therefore the system to be quasi-static.

During initial implementation of any UHDR irradiation protocol, it is highly recommended that the physician and the physicist be present at the machine to review and approve pre-treatment images, as suggested for instance for intraoperative RT (IORT) by the ESTRO IORT Task Force [76].

Treatment delivery verification

An on-line imaging system and/or an in vivo dosimetry system is strongly recommended for UHDR-RT to be kept as a record of treatment delivery.

On-line fluoroscopy could be one example of such an imaging system used in combination with an in vivo dosimetry system, such as film or point scintillators to record the doses [77-80]. On-line active detectors based on technology such as radiation optics and ionizing radiation acoustic

imaging, which are capable of pulse-based detection, are an appealing alternative for on-line patient dose- and dose rate monitoring.

4. Quality assurance and dosimetry protocols

The establishment of a medical physics QA program is mandatory when introducing a new RT modality to clinics. QA is commonly sub-divided into QA of machines, image-guided RT devices, treatment planning systems, record and verify systems, and patient-specific QA programs and procedures. Recommendations and guidelines for QA procedures for conventional RT [81-96] provide the baseline that should be consistently extended to cover UHDR-specific factors and ensure safe clinical translation of UHDR-RT. In particular, beam parameters characterizing temporal aspects of dose delivery need to be included in testing protocols and evaluation criteria. The beam parameters that should be accounted for include average dose rates, instantaneous dose rates, pulse characteristics (repetition frequency, width, amplitude), as well as timing of scanned or intensity-modulated beam delivery. The significance of each of these beam parameters regarding the triggering and magnitude of the FLASH effect in normal tissues is an important aspect that still needs to be addressed. Therefore, suitable dosimetric methods and detection systems should be implemented accordingly.

Recommendations on treatment planning system and machine QA for electron and proton beams in UHDR-RT are outside the scope of this report. However, based on recent publications [10, 15, 55, 97], machine commissioning in UHDR facilities should be performed according to conventional RT commissioning practices, that is, by varying the beam parameters, such as average and instantaneous dose rate and pulse characteristics, in order to check the extent to which the beam characteristics (short- and long-term stability, beam profile, and percent depth dose curves) depend on dose-rate related quantities. Additionally, the periodicity of machine- and patient-specific QA practices and tolerances will depend on the system in use and will be defined after acceptance tests and the commissioning procedures. In this document, we focus primarily on patient-specific safety concerns, not individual steps of the RT chain.

To date, there are no well-established common standards for UHDR reference dosimetry protocols as they exist for conventional dose rate RT (TG-51 [94], TG-25 [95], TRS-398 [98]). The design and evaluation of dedicated dosimeters and phantoms for different types of QA procedures is currently an active area of research. In parallel, other working groups such as AAPM TG-359 [27]

and the EURAMET consortium UHDPulse [26] have been set up to define the recommendations for dosimetry of UHDR-RT and to advance dosimetry metrology for UHDR-RT, respectively. Ionization chambers which are widely used as reference dosimeters in conventional RT, exhibit significant saturation effects due to ion recombination that decreases their efficiency in UHDR beams [55, 99-102]. Reliable and robust active detectors are the key instruments required for every-day clinical dosimetry measurements. Recently, new prototypes of ionization chambers [94-96], diamond-based detectors [106, 107], and calorimeters [46] have been shown to be promising candidates for secondary standard instruments. These detectors are on-line devices, but they require a calibration against a primary standard instrument. Such calibrations are typically carried out under reference conditions. However, the reference conditions have not yet been defined for UHDR exposures. Some national metrology institutes have established UHDR electron radiation facilities that enable direct calibration of the secondary instrument in a primary standard laboratory [108, 109] with traceability to a relevant primary standard [110]. Others employ portable primary standard calorimeters [111] to carry out calibrations directly in a user beam [104112]. Nevertheless, to date, calibration services for UHDR-RT are not available, as metrology approaches are still under development. More guidelines will be available within the next few years [27, 113]. In the meantime, it is still recommended to employ the redundant passive dosimetry systems that have already been evaluated and used in UHDR dosimetry studies [114, 115], such as radiochromic films, thermoluminescent dosimeters, and alanine dosimeters.

Regarding phantoms, commercially available homogeneous and anthropomorphic phantoms with insert cavities for radiochromic films and detector arrays, such as alanine pellets or scintillators [78], should be viable options. However, care needs to be taken because prolonged exposure to UHDR beams can lead to charge build-up in a phantom [116], which can affect detector response and the properties of the material. UHDR-induced radiation damage should be considered when purchasing equipment.

For each UHDR-RT setting of a clinical machine suitable for either external beam irradiation or IORT (superficial tumors or deep-seated tumor), dosimetry intercomparison with other institutes is strongly recommended, until dosimetric audits for a reference beam in an anthropomorphic phantom are available.

Patient -specific plan QA

Plan verification QA of any UHDR-RT technique must always be performed before treatment delivery. Since UHDR-RT will be likely delivered in a single high-dose fraction or in a hypofractionated regimen, we recommend using the same evaluation criteria as those used for stereotactic treatments. It is still unknown which FLASH predictors will be used in UHDR treatment prescriptions; a full spectrum of approaches have been proposed in the literature, ranging from only average dose rate and irradiation time [5] to FLASH-effectiveness maps [117]. Therefore, future patient-specific QA evaluation procedures may include additional quantities, such as the spatial distribution of dose rates [118, 119] and/or cumulative histograms of instantaneous or average dose rates, which might allow us to validate the FLASH effect in healthy tissue. The use of active dosimetric systems might be desirable for quick processing of plan verifications. Some prototypes for animal experiments have already been proposed [80].

In vivo dosimetry

In vivo dosimetry is strongly recommended when it is clinically feasible (e.g., superficial treatment or IORT). Among other methods, delivered dose reporting can be useful in retrospective studies to identify correlations with acute and late tissue toxicity and to better understand the FLASH effect. The use of dose-rate independent passive dosimeters is justified adequate for reporting the dose delivered to the patient, as required by EC Council directive 2013/59/EURATOM [30]. Active detectors for in vivo dosimetry would be desirable for improved operational efficiency. Ideally, the active detector should also be able to measure the dose-rate in real-time. Finally, it is of paramount importance that the use of in vivo dosimetric systems, as in conventional RT, does not cause substantial perturbations to the administered dose distributions.

Patient registry and reporting system

As dozens of institutions embark on small-scale UHDR studies, we recommend that the UHDR community establishes, populates, and maintains a UHDR patient registry that pools relevant patient, treatment, and outcome data in a central repository to allow investigators to compare techniques, and improve statistics for short-term and long-term outcome analyses. The registry could be modelled after those that have been established for proton therapy, such as the Proton Collaborative Group (PCG) and the Proton and Photon Consortium Registry [120].

From a safety perspective, an international, on-line UHDR incident reporting system to which users can report machine errors or misadministration would also be a valuable tool for the UHDR-RT community.

Minimum and optimal requirements for clinical safety

The minimum and optimal requirements for UHDR clinical safety are summarized in table 1. Minimum requirements refer to the state of the art for safe clinical implementation, while optimal requirements should be met when specific devices become available in the future. Specific requirements for beam monitoring have been defined for collimated broad beam delivery and for sequential beam delivery, regardless of the irradiation modality. Collimated broad beam delivery includes HEE beams and particles/VHEE scattering techniques, while sequential beam delivery includes PBS particle beams or intensity-modulated beams and multi-field delivery.

5. Conclusion

Besides its principal aim, patient safety, the safe implementation of UHDR will be imperative for obtaining high-quality outcome data as we explore the potential clinical benefits of UHDR-RT. This ESTRO working group paper highlights important and specific recommendations that the radiation oncology community should strive to adopt and follow. These recommendations will harmonize and standardize important aspects of UHDR-RT for patient safety when implementing this new-paradigm treatment modality. This paper delineates recommendations related to (1) safety, radiation protection, and regulation, (2) simulation, in-room image guidance and treatment delivery verification, and (3) quality assurance and dosimetry protocols, with the goal of assisting in the safe translation and implementation of UHDR-RT in the clinic.

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Bibliography

[1] O. Gaide, F. Herrera, W. Jeanneret Sozzi, P. Goncalves Jorge, R. Kinj, C. Bailat, et al. Comparison of ultra-high versus conventional dose rate radiotherapy in a patient with cutaneous lymphoma. Radiother Oncol. 2022; 174: 87-91

[2] M. C. Vozenin, J. H. Hendry, and C. L. Limoli. Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken, *Clin Oncol (R Coll Radiol),* vol. 31, no. 7, pp. 407-415, 2019

[3] A. A. Friedl, K. M. Prise, K. T. Butterworth, P. Montay-Gruel, and V. Favaudon. Radiobiology of the FLASH effect. *Medical Physics,* vol. 49, pp. 1993-2013, 2022

[4] T. T. Böhlen *et al.* Normal Tissue Sparing by FLASH as a Function of Single-Fraction Dose: A Quantitative Analysis. *International Journal of Radiation Oncology* Biology* Physics,* vol. 114, no. 5, pp. 1032-1044, 2022

[5] J. Bourhis *et al.* Treatment of a first patient with FLASH-radiotherapy, *Radiother Oncol,* vol. 139, pp. 18-22, 2019

[6] A. E. Mascia *et al.* Proton FLASH radiotherapy for the treatment of symptomatic bone metastases: the FAST-01 nonrandomized trial," *JAMA oncology,* vol. 9, no. 1, pp. 62-69, 2023

[7] M.-C. Vozenin *et al.*The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients,*Clinical Cancer Research,* vol. 25, no. 1, pp. 35-42, 2019

[8] M. Rahman, A. Trigilio, G. Franciosini, R. Moeckli, R. Zhang, and T. T. Böhlen. FLASH radiotherapy treatment planning and models for electron beams, *Radiotherapy and Oncology,* 2022

[9] V. F. P. Lansonneur, S. Heinrich, C. Fouillade, P. Verrelle, L. De Marzi. Simulation and experimental validation of a prototype electron beam linear accelerator for preclinical studies. *Physica Medica,* pp. 50-57, 2019

[10] R. Moeckli *et al.* Commissioning of an ultra-high dose rate pulsed electron beam medical LINAC for FLASH RT preclinical animal experiments and future clinical human protocols,*Medical physics,* vol. 48, no. 6, pp. 3134-3142, 2021

[11] M. G. Ronga *et al.* Back to the Future: Very High-Energy Electrons (VHEEs) and Their Potential Application in Radiation Therapy, *Cancers,* vol. 13, no. 19, p. 4942, 2021 [Online]. Available: https://www.mdpi.com/2072-6694/13/19/4942.

[12] L. Faillace *et al.* Compact S-band linear accelerator system for ultrafast, ultrahigh dose-rate radiotherapy, *Physical Review Accelerators and Beams,* vol. 24, no. 5, 2021

[13] P. Montay-Gruel, S. Corde, J. A. Laissue, and M. Bazalova-Carter. FLASH radiotherapy with photon beams, *Medical Physics,* vol. 49, no. 3, pp. 2055-2067, 2022

[14] H. O. Simon Jolly, M. Schippers, C. Welsch.Technical challenges for FLASH proton therapy,*Physica Medica,* pp. 71-82, 2020

[15] E. S. Diffenderfer *et al.* Design, implementation, and in vivo validation of a novel proton FLASH radiation therapy system, *International Journal of Radiation Oncology* Biology* Physics,* vol. 106, , pp. 440-448, 2020

[16] S. Wei *et al.* FLASH radiotherapy using single-energy proton PBS transmission beams for hypofractionation liver cancer: Dose and dose rate quantification, *Frontiers in Oncology,* vol. 11, p. 5757, 2022

[17] U. A. Weber, E. Scifoni, and M. Durante.FLASH radiotherapy with carbon ion beams. *Medical Physics,* vol. 49, pp. 1974-1992, 2022

[18] P.A Taylor. et al. *A* roadmap to clinical trials for FLASH. Med Phys, 2022. **49**(6): p. 4099-4108

[19] W. Zou et al. Framework for Quality Assurance of Ultrahigh Dose Rate Clinical Trials Investigating FLASH Effects and Current Technology Gaps. International Journal of Radiation Oncology*Biology*Physics, 2023. **116**(5): p. 1202-1217

[20] IAEA, *Relative biological effectiveness in ion beam therapy*. International Atomic Energy Agency, 2008

[21] IEC 60976:2007 Medical electrical equipment—Medical electron accelerators—Functional performance characteristics.

[22] IEC 60977:2008, Medical electrical equipment—Medical electron accelerators—Guidelines for functional performance characteristics.

[23] IEC 62667:2017, Medical electrical equipment - Medical light ion beam equipment - Performance characteristics.

[24] EN IEC 60601-2-1:2020 Medical electrical equipment-Part 2-1: Particular requirements for the basic safety and essential performance of electron accelerators in the range 1 to 50 MeV.

[25] IEC 60601-2-64:2014 Medical electrical equipment - Part 2-64: Particular requirements for the basic safety and essential performance of light ion beam medical electrical equipment.

[26] *http://uhdpulse-empir.eu/*.

[27] Task Group No. 359 - FLASH (ultra-high dose rate) radiation dosimetry (TG359).

[28] IAEA, Applying radiation safety standards in radiotherapy, Report n°38, 2006

[29] T. Q. Tran, S. Jeong, and K. N. H. Nguyen. NCRP Report 151 Structural shielding design and evaluation for megavoltage x-and gamma-ray radiotherapy facilities, 2006

[30] Council Directive 2013/59/EURATOM of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation.

[31] J. Malicki, K. Przybylska, A. Jahnen, J. Godet, M. Valero, and M. Bulot.Radiation Protection nº181: General guidelines on risk management in external beam radiotherapy,*European Commission, Luxembourg,* 2015

[32] Y. Yonekura *et al.* ICRP publication 127: radiological protection in ion beam radiotherapy,*Annals of the ICRP,* vol. 43, no. 4, pp. 5-113, 2014

[33] Bourhis, J., et al. Clinical translation of FLASH radiotherapy: Why and how? Radiotherapy and Oncology, 2019. 139: p. 11-17

[34] Esplen N, Mendonca MS, Bazalova-Carter M. Physics and biology of ultrahigh dose-rate (FLASH) radiotherapy: a topical review. Phys Med Biol. 2020 Dec 4;65(23)

[35] Byrne KE et al. Technical note: A small animal irradiation platform for investigating the dependence of the FLASH effect on electron beam parameters. Med Phys. 2024

[36] Saade, G., et al., Ultrahigh-Dose-Rate Proton Irradiation Elicits Reduced Toxicity in Zebrafish Embryos. Adv Radiat Oncol, 2023. 8(2): p. 101124

[37] Böhlen, T.T., et al., In Reply to Horst et al. International Journal of Radiation Oncology*Biology*Physics, 2023. 115(4): p. 1007-1009

[38] A. J. Cetnar and D. J. DiCostanzo. The lifetime of a linac monitor unit ion chamber, *Journal of Applied Clinical Medical Physics,* vol. 22, no. 12, pp. 108-114, 2021

[39] G. Klimpki *et al* .A beam monitoring and validation system for continuous line scanning in proton therapy, *Physics in Medicine & Biology,* vol. 62, no. 15, p. 6126, 2017

[40] F. Di Martino *et al.* FLASH Radiotherapy With Electrons: Issues Related to the Production, Monitoring, and Dosimetric Characterization of the Beam. *Frontiers in Physics,* Original Research vol. 8, 2020

[41] S. Rossomme *et al.* Ion recombination correction factor in scanned light-ion beams for absolute dose measurement using plane-parallel ionisation chambers, *Physics in Medicine & Biology,* vol. 62, no. 13, p. 5365, 2017

[42] E. Konradsson *et al.* Correction for ion recombination in a built-in monitor chamber of a clinical linear accelerator at ultra-high dose rates, *Radiation research,* vol. 194, pp. 580-586, 2020

[43] J. D. Wilson, E. M. Hammond, G. S. Higgins, and K. Petersson, Ultra-high dose rate (FLASH) radiotherapy: silver bullet or fool's gold?, *Frontiers in oncology,* vol. 9, p. 1563, 2020

[44] P. Montay-Gruel *et al.* Ultra-high-dose-rate FLASH irradiation limits reactive gliosis in the brain, *Radiation research,* vol. 194, no. 6, pp. 636-645, 2020

[45] F. Romano, C. Bailat, P. G. Jorge, M. L. F. Lerch, A. Darafsheh Ultra-high dose rate dosimetry: Challenges and opportunities for FLASH radiation therapy. Medical Physics 2023

[46] A. Subiel and F- Romano. Recent developments in absolute dosimetry for FLASH radiotherapy. British Journal of Radiology, Volume 96, Issue 1148, 2023

[47] E. Schüler *et al.* Experimental platform for ultra-high dose rate FLASH irradiation of small animals using a clinical linear accelerator, *International Journal of Radiation Oncology* Biology* Physics,* vol. 97, no. 1, pp. 195-203, 2017

[48] M. Lempart *et al.* Modifying a clinical linear accelerator for delivery of ultra-high dose rate irradiation, *Radiotherapy and Oncology,* vol. 139, pp. 40-45, 2019

[49] M. Rahman *et al.* Electron FLASH delivery at treatment room isocenter for efficient reversible conversion of a clinical LINAC, *International Journal of Radiation Oncology* Biology* Physics,* vol. 110, no. 3, pp. 872-882, 2021

[50] P. Goncalves Jorge *et al.* Validation of an ultrahigh dose rate pulsed electron beam monitoring system using a current transformer for FLASH preclinical studies, *Medical Physics,* vol. 49, no. 3, pp. 1831-1838, 2022

[51] R. Oesterle *et al.* Implementation and validation of a beam-current transformer on a medical pulsed electron beam LINAC for FLASH-RT beam monitoring, *Journal of Applied Clinical Medical Physics,* vol. 22, no. 11, pp. 165-171, 2021

[52] K. Liu *et al.* Dual beam-current transformer design for monitoring and reporting of electron ultra-high dose rate (FLASH) beam parameters, *Journal of Applied Clinical Medical Physics,* p. e13891, 2023

[53] C. Waters, Current transformers provide accurate, isolated measurements, *Power conversion & intelligent motion,* vol. 12, no. 12, 1986

[54] K. Kokurewicz *et al.* An experimental study of focused very high energy electron beams for radiotherapy, *Communications Physics,* vol. 4, no. 1, p. 33, 2021

[55] Y. Simeonov *et al.*3D range-modulator for scanned particle therapy: development, Monte Carlo simulations and experimental evaluation," *Physics in Medicine & Biology,* vol. 62, no. 17, p. 7075, 2017.

[56] M. Schwarz, E. Traneus, S. Safai, A. Kolano, and S. van de Water.Treatment planning for Flash radiotherapy: General aspects and applications to proton beams,*Medical Physics,* vol. 49, no. 4, pp. 2861-2874, 2022

[57] Y. Simeonov *et al.*Monte Carlo simulations and dose measurements of 2D range-modulators for scanned particle therapy,*Zeitschrift für Medizinische Physik,* vol. 31, no. 2, pp. 203-214, 2021

[58] S. Rana, J. Bennouna, A. N. Gutierrez, and A. B. Rosenfeld. Impact of magnetic field regulation in conjunction with the volumetric repainting technique on the spot positions and beam range in pencil beam scanning proton therapy, *Journal of Applied Clinical Medical Physics,* vol. 21, no. 11, pp. 124-131, 2020

[59] P. Chaudhary *et al.*Radiobiology experiments with ultra-high dose rate laser-driven protons: methodology and state-of-the-art,*Frontiers in Physics,* vol. 9, p. 624963, 2021

[60] J. Bin *et al.* A new platform for ultra-high dose rate radiobiological research using the BELLA PW laser proton beamline,*Scientific reports,* vol. 12, no. 1, p. 1484, 2022

[61] F. Kroll *et al.* Tumour irradiation in mice with a laser-accelerated proton beam,*Nature Physics,* vol. 18, no. 3, pp. 316-322, 2022

[62] A. Berne, K. Petersson, I. D. Tullis, R. G. Newman, and B. Vojnovic. Monitoring electron energies during FLASH irradiations, *Physics in Medicine & Biology,* vol. 66, no. 4, p. 045015, 2021

[63] M. Jaccard *et al.* High dose-per-pulse electron beam dosimetry: commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use,*Medical physics,* vol. 45, no. 2, pp. 863-874, 2018

[64] Y. Poirier *et al.* Radiation shielding and safety implications following linac conversion to an electron FLASH-RT unit, *Medical Physics,* vol. 48, no. 9, pp. 5396-5405, 2021

[65] M. Caresana *et al.*Intercomparison of radiation protection instrumentation in a pulsed neutron field,*Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment,* vol. 737, pp. 203-213, 2014

[66] I. Oraiqat *et al.* An ionizing radiation acoustic imaging (iRAI) technique for real-time dosimetric measurements for FLASH radiotherapy, *Medical physics,* vol. 47, no. 10, pp. 5090-5101, 2020

[67] M. Rahman *et al.* Spatial and temporal dosimetry of individual electron FLASH beam pulses using radioluminescence imaging, *Physics in Medicine & Biology,* vol. 66, no. 13, p. 135009, 2021

[68] I. El Naqa, B. W. Pogue, R. Zhang, I. Oraiqat, and K. Parodi. Image guidance for FLASH radiotherapy, *Medical Physics,* vol. 49, no. 6, pp. 4109-4122, 2022

[69] L. Gilbeau, M. Octave-Prignot, T. Loncol, L. Renard, P. Scalliet, and V. Grégoire. Comparison of setup accuracy of three different thermoplastic masks for the treatment of brain and head and neck tumors,*Radiotherapy and Oncology,* vol. 58, no. 2, pp. 155-162, 2001

[70] A. J. Wroe, D. A. Bush, R. W. Schulte, and J. D. Slater. Clinical immobilization techniques for proton therapy,*Technology in Cancer Research & Treatment,* vol. 14, no. 1, pp. 71-79, 2015

[71] H. A. Al-Hallaq *et al.* AAPM task group report 302: Surface-guided radiotherapy, *Medical physics,* vol. 49, no. 4, pp. e82-e112, 2022

[72] H. Li *et al.*Report of AAPM Task Group 290: Respiratory motion management for particle therapy, *Medical Physics,* 2022

[73] P. J. Keall *et al.* The management of respiratory motion in radiation oncology report of AAPM Task Group 76 a, *Medical physics,* vol. 33, no. 10, pp. 3874-3900, 2006

[74] J. M. Slagowski *et al.* Evaluation of the visibility and artifacts of 11 common fiducial markers for image guided stereotactic body radiation therapy in the abdomen, *Practical radiation oncology,* vol. 10, no. 6, pp. 434-442, 2020

[75] S. P. McCullough *et al.* AAPM MEDICAL PHYSICS PRACTICE GUIDELINE 2. b.: Commissioning and quality assurance of X-ray-based image-guided radiotherapy systems, *Journal of Applied Clinical Medical Physics,* vol. 22, no. 9, pp. 73-81, 2021

[76] G. Fastner *et al.* ESTRO IORT Task Force/ACROP recommendations for intraoperative radiation therapy with electrons (IOERT) in breast cancer, *Radiotherapy and Oncology,* vol. 149, pp. 150-157, 2020

[77] A. Beddar, T. Mackie, and F. Attix. Water-equivalent plastic scintillation detectors for high-energy beam dosimetry: I. Physical characteristics and theoretical considerations, *Physics in Medicine & Biology,* vol. 37, no. 10, p. 1883, 1992

[78] F. Therriault-Proulx, L. Archambault, L. Beaulieu, and S. Beddar. Development of a novel multi-point plastic scintillation detector with a single optical transmission line for radiation dose measurement, *Physics in Medicine & Biology,* vol. 57, no. 21, p. 7147, 2012

[79] L. Beaulieu and S. Beddar. Review of plastic and liquid scintillation dosimetry for photon, electron, and proton therapy, *Physics in Medicine & Biology,* vol. 61, no. 20, p. R305, 2016

[80] E. Kanouta, J. G. Johansen, G. Kertzscher, M. K. Sitarz, B. S. Sørensen, and P. R. Poulsen. Time structure of pencil beam scanning proton FLASH beams measured with scintillator detectors and compared with log files,*Medical Physics,* vol. 49, no. 3, pp. 1932-1943, 2022

[81] H. Palmans, P. Andreo, M. S. Huq, J. Seuntjens, K. E. Christaki, and A. Meghzifene. Dosimetry of small static fields used in external photon beam radiotherapy: summary of TRS-483, the IAEA–AAPM international Code of Practice for reference and relative dose determination, *Medical physics,* vol. 45, no. 11, pp. e1123-e1145, 2018

[82] P. R. Almond *et al.* The calibration and use of plane-parallel ionization chambers for dosimetry of electron beams: An extension of the 1983 AAPM protocol report of AAPM Radiation Therapy Committee Task Group No. 39, *Medical physics,* vol. 21, no. 8, pp. 1251-1260, 1994

[83] A. S. Beddar *et al.* Intraoperative radiation therapy using mobile electron linear accelerators: report of AAPM Radiation Therapy Committee Task Group No. 72, *Medical physics,* vol. 33, no. 5, pp. 1476-1489, 2006

[84] I. J. Das *et al.*Accelerator beam data commissioning equipment and procedures: report of the TG-106 of the Therapy Physics Committee of the AAPM, *Medical physics,* vol. 35, no. 9, pp. 4186-4215, 2008

[85] E. E. Klein *et al.* Task Group 142 report: Quality assurance of medical accelerators a, *Medical physics,* vol. 36, no. 9Part1, pp. 4197-4212, 2009

[86] B. Mijnheer and D. Georg.ESTRO booklet no. 9: guidelines for the verification of IMRT, 2008, *Back to cited text,* no. 6, 2008

[87] B. Arjomandy *et al.*AAPM task group 224: comprehensive proton therapy machine quality assurance, *Medical physics,* vol. 46, no. 8, pp. e678-e705, 2019

[88] I. Chetty, *et al.* Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning, *Med. Phys,* vol. 34, no. 12, p. 4818, 2007

[89] J. B. Smilowitz *et al.* AAPM medical physics practice guideline 5. a.: commissioning and QA of treatment planning dose calculations—megavoltage photon and electron beams, *Journal of applied clinical medical physics,* vol. 16, no. 5, pp. 14-34, 2015

[90] G. Cranmer-Sargison. Dosimetry of small static fields used in external beam radiotherapy: a review of IAEA TRS 483, *Journal of Medical Physics,* vol. 43, no. suppl. 1, p. 1, 2018

[91] I. TecDoc, 1583: commissioning of radiotherapy treatment planning systems: testing for typical external beam treatment techniques,"*Vienna: International Atomic Energy Agency,* 2008.

[92] B. Fraass *et al.* American Association of Physicists in Medicine Radiation Therapy Committee Task Group 53: quality assurance for clinical radiotherapy treatment planning, *Medical physics,* vol. 25, no. 10, pp. 1773-1829, 1998

[93] E. B. Podgorsak. Treatment machines for external beam radiotherapy, *Radiation Oncology Physics: A Handbook for Teachers and Students. IAEA, Vienna, Austria,* pp. 123-160, 2005

[94] P. R. Almond *et al.* AAPM's TG-51 protocol for clinical reference dosimetry of high-energy photon and electron beams, *Medical physics,* vol. 26, no. 9, pp. 1847-1870, 1999

[95] B. J. Gerbi *et al.* Recommendations for clinical electron beam dosimetry: supplement to the recommendations of Task Group 25, *Medical physics,* vol. 36, no. 7, pp. 3239-3279, 2009

[96] P. Andreo *et al.* INTERNATIONAL ATOMIC ENERGY AGENCY, Absorbed Dose Determination in External Beam Radiotherapy. An International Code of Practice for Dosimetry Based on Standards of Absorbed Dose to Water,Technical Report Series.

[97] K. P. Nesteruk *et al.* Commissioning of a clinical pencil beam scanning proton therapy unit for ultra-high dose rates (FLASH), *Medical physics,* vol. 48, no. 7, pp. 4017-4026, 2021

[98] *Absorbed Dose Determination in External Beam Radiotherapy*. Vienna: INTERNATIONAL ATOMIC ENERGY AGENCY, 2001

[99] M. McManus *et al.* The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams, *Scientific reports,* vol. 10, no. 1, p. 9089, 2020

[100] A. Subiel *et al.* Challenges of dosimetry of ultra-short pulsed very high energy electron beams, *Physica Medica,* vol. 42, pp. 327-331, 2017

[101] K. Petersson *et al.* High dose-per-pulse electron beam dosimetry—a model to correct for the ion recombination in the Advanced Markus ionization chamber, *Medical physics,* vol. 44, no. 3, pp. 1157-1167, 2017

[102] M. Gotz, L. Karsch, and J. Pawelke. A new model for volume recombination in plane-parallel chambers in pulsed fields of high dose-per-pulse, *Physics in Medicine & Biology,* vol. 62, no. 22, p. 8634, 2017

[103] F. Gómez *et al.* Development of an ultra-thin parallel plate ionization chamber for dosimetry in FLASH radiotherapy, *Medical Physics,* vol. 49, no. 7, pp. 4705-4714, 2022

[104] R. Kranzer *et al.* Charge collection efficiency, underlying recombination mechanisms, and the role of electrode distance of vented ionization chambers under ultra-high dose-per-pulse conditions, *Physica Medica,* vol. 104, pp. 10-17, 2022

[105] F. Di Martino F. *et al.* A new solution for UHDP and UHDR (Flash) measurements: Theory and conceptual design of ALLS chamber. Phys Med. 2022 ;102:9-18.

[106] M. Marinelli, G. Felici, F. Galante, A. Gasparini, L. Giuliano, S. Heinrich, *et al*. Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry. Medical Physics Medical Physics, vol 49, pp. 1902-1910, 2022.

[107] G. Verona Rinatihttps://aapm.onlinelibrary.wiley.com/authored-by/Verona+Rinati/Gianluca, G. Felici, F. Galante , A. Gasparini , R. Kranzer , G. Mariani ,et al. Application of a novel diamond detector for commissioning of FLASH radiotherapy electron beams. Med *Phys.* 2022; 49: 5513- 5522.

[108] A. Schüller, S. Pojtinger, M. Meier, C. Makowski, and R.P. Kapsch. The metrological electron accelerator facility (MELAF) for research in dosimetry for radiotherapy, in *World Congress on Medical Physics and Biomedical Engineering 2018: June 3-8, 2018, Prague, Czech Republic (Vol. 3)*, 2019: Springer, pp. 589-593.

[109] A. Bourgouin, A. Knyziak, M. Marinelli, R. Kranzer, A. Schüller, and R.-P. Kapsch. Characterization of the PTB ultra-high pulse dose rate reference electron beam, *Physics in Medicine & Biology,* vol. 67, no. 8, p. 085013, 2022

[110] A. Bourgouin. The PTB water calorimeter for determining the absolute absorbed dose to water in ultra-high pulse dose rate electron beams, PMB, under review, 2023

[111] A. Lourenço *et al.* Application of a portable primary standard level graphite calorimeter for absolute dosimetry in a clinical low-energy passively scattered proton beam, *Physics in Medicine & Biology,* vol. 67, no. 22, p. 225021, 2022

[112] A. Lourenço *et al.* Absolute dosimetry for FLASH proton pencil beam scanning radiotherapy, *Scientific Reports,* vol. 13, no. 1, p. 2054, 2023

[113] A. Schüller *et al.*T he European Joint Research Project UHDpulse–Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates, *Physica Medica,* vol. 80, pp. 134-150, 2020

[114] P. G. Jorge *et al.* Dosimetric and preparation procedures for irradiating biological models with pulsed electron beam at ultra-high dose-rate, *Radiother Oncol,* vol. 139, pp. 34-39, Oct 2019.
[115] M. Togno *et al.* Ultra-high dose rate dosimetry for pre-clinical experiments with mm-small proton fields, *Phys Med,* vol. 104, pp. 101-111, Dec 2022
[116] L. Mattsson and H. Svensson. Charge build-up effects in insulating phantom materials, *Acta Radiologica: Oncology,* vol. 23, no. 5, pp. 393-399, 1984
[117] M. Krieger *et al.* A quantitative FLASH effectiveness model to reveal potentials and pitfalls of high dose rate proton therapy, *Medical physics,* vol. 49, no. 3, pp. 2026-2038, 2022
[118] P. van Marlen, M. Dahele, M. Folkerts, E. Abel, B. J. Slotman, and W. F. Verbakel. Bringing FLASH to the clinic: treatment planning considerations for ultrahigh dose-rate proton beams, *International Journal of Radiation Oncology* Biology* Physics,* vol. 106, no. 3, pp. 621-629, 2020
[119] S. Van De Water, S. Safai, J. M. Schippers, D. C. Weber, and A. J. Lomax. Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates, *Acta oncologica,* vol. 58, no. 10, pp. 1463-1469, 2019
[120] https://pcgresearch.org/.