Received: 23 April 2023 | Revised: 7 October 2023 | Accepted: 31 October 2023

DOI: 10.1002/mp.16854

RESEARCH ARTICLE

MEDICAL PHYSICS

Multi-institutional consensus on machine QA for isochronous cyclotron-based systems delivering ultra-high dose rate (FLASH) pencil beam scanning proton therapy in transmission mode

Kees Spruijt[1,2] | **Sina Mossahebi**[3] | **Haibo Lin**[4] | **Eunsin Lee**[5] | **James Kraus**[6] | **Anees Dhabaan**[7] | **Per Poulsen**[8] | **Matthew Lowe**[9] | **Ahmet Ayan**[10] | **Sylvie Spiessens**[11] | **Jeremy Godart**[1,2] | **Mischa Hoogeman**[1,2]

[1]HollandPTC, Delft, The Netherlands

[2]Department of Radiotherapy, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, The Netherlands

[3]Department of Radiation Oncology, University of Maryland School of Medicine, Baltimore, Maryland, USA

[4]New York Proton Center, New York, New York, USA

[5]Department of Radiation Oncology, University of Cincinnati, Cincinnati, Ohio, USA

[6]Department of Radiation Oncology, University of Alabama-Birmingham, Birmingham, Alabama, USA

[7]Department of Radiation Oncology, Emory University of Medicine, Atlanta, Georgia, USA

[8]Danish Center for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark and Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[9]Christie Medical Physics and Engineering, The Christie NHS Foundation Trust, Manchester, UK

[10]Department of Radiation Oncology, Ohio State University Medical Center, Columbus, Ohio, USA

[11]Varian, a Siemens Healthineers Company, Groot-Bijgaarden, Belgium

Correspondence
Kees Spruijt, HollandPTC, Huismansingel 4, 2629JH Delft, The Netherlands.
Email: k.spruijt@hollandptc.nl

Abstract

Background: The first clinical trials to assess the feasibility of FLASH radiotherapy in humans have started (FAST-01, FAST-02) and more trials are foreseen. To increase comparability between trials it is important to assure treatment quality and therefore establish a standard for machine quality assurance (QA). Currently, the AAPM TG-224 report is considered as the standard on machine QA for proton therapy, however, it was not intended to be used for ultra-high dose rate (UHDR) proton beams, which have gained interest due to the observation of the FLASH effect.

Purpose: The aim of this study is to find consensus on practical guidelines on machine QA for UHDR proton beams in transmission mode in terms of which QA is required, how they should be done, which detectors are suitable for UHDR machine QA, and what tolerance limits should be applied.

Methods: A risk assessment to determine the gaps in the current standard for machine QA was performed by an international group of medical physicists. Based on that, practical guidelines on how to perform machine QA for UHDR proton beams were proposed.

Results: The risk assessment clearly identified the need for additional guidance on temporal dosimetry, addressing dose rate (constancy), dose spillage, and scanning speed. In addition, several minor changes from AAPM TG-224 were identified; define required dose rate levels, the use of clinically relevant dose levels, and the use of adapted beam settings to minimize activation of detector and phantom materials or to avoid saturation effects of specific detectors. The final report was created based on discussions and consensus.

Conclusions: Consensus was reached on what QA is required for UHDR scanning proton beams in transmission mode for isochronous cyclotron-based systems and how they should be performed. However, the group discussions also showed that there is a lack of high temporal resolution detectors and sufficient QA data to set appropriate limits for some of the proposed QA procedures.

KEYWORDS
FLASH, machine QA, ultra-high dose rate

1 | INTRODUCTION

Despite efforts to advance radiotherapy treatment of tumor volumes while sparing healthy tissue by means of fractionation, image guidance and more conformal radiotherapy treatments, radiotherapy can still result in severe toxicity in healthy tissue in some cancer treatments. This toxicity could potentially be decreased while maintaining tumor control by using ultra high dose rate (UHDR) delivery along with a high dose per fraction — the so-called FLASH effect. Most experiments have been performed in animal models[1–3] though a small number of human patients have been treated with UHDR deliveries.[4,5] Typically, dose rates of > 40 Gy/s have been set to reach the FLASH effect. Currently, most of the FLASH data are based on UHDR pulsed electron beam studies. However, these electron beams are limited to superficial targets due to low tissue penetration. On the other hand, UHDR proton beams allow the irradiation of deep-seated tumors and have become readily available for several proton therapy facilities with minor modifications in the system. The first in-human FLASH clinical trial (FAST-01) has already been completed using a cyclotron-based pencil beam scanning proton beam.[6] As additional patient studies are expected to be conducted in a variety of centers over the world, it is important to assure a safe and standardized treatment quality to facilitate a fair comparison between each center's data. Since current reports on machine quality assurance (QA) were written at a time when dose rate had limited clinical importance, there is a need to evaluate and adapt current QA procedures in the context of our new understanding of the FLASH effect.

Currently, "shoot-through" or transmission proton beams are mostly used for preclinical research and first patient treatments. For these beams, the maximum current at the nozzle can be obtained by fully retracting the energy degrader in the energy selection system. Another option is the Bragg Peak FLASH technique using the same 250 MeV beam. However, this technique requires beam modifiers to create a spread-out Bragg Peak (SOBP) and adjust the range of the SOBP based on the target location. A promising solution for the beam modifier is a ridge filter.[7] The focus of this report is on transmission beams only as this mode has been commonly used.

The routine machine QA of most proton delivery systems is based on a report of the American Association of Physicists in Medicine, AAPM TG-224.[8] In this report, only conventional dose rate proton beams were considered. Therefore, further consideration is required to assess its applicability to UHDR proton beams. In the context of FLASH radiotherapy, dose rate verification has become an important factor along with existing considerations such as dose and geometric accuracy. Furthermore, there are also various practical challenges such as the dose rate dependency of commonly used detectors, the limited availability of time resolved detectors and higher radiation protection concerns regarding activation of detectors and phantoms due to the very high dose rates involved.

Since the FLASH effect and UHDR beams are recent developments, only a limited number of machine QA related publications and protocols are available. Most early publications addressed the saturation effect of ionization chambers intended for reference dosimetry which have proven to be relevant to the pulsed structure of electron beams.[9,10] However, as demonstrated by Yang et al. and Lee et al.,[11,12] the charge saturation for specific ionization chambers appears to be less significant for quasi-continuous proton beams with nozzle currents of up to 215 nA even when standard bias voltage is used. Moreover, novel detectors have been designed and evaluated,[12–14] but further developments are still required to improve the characterization and QA of the UHDR proton beam.

This report aims to give practical guidelines on how to perform QA on UHDR proton beams based on current practices and knowledge. An international group of experts, all Varian ProBeam users, gathered in multiple sessions to form the basis of this report. In the first step, a risk assessment was performed to determine the gaps in the current code of practice, taking the AAPM TG-224 report as a reference. The second step was to determine, based on experiences and discussions, how to fill in those missing gaps, providing suggestions on how to perform QA, which detectors to use and what tolerance levels to apply.

2 | DEFINITIONS

An overview of definitions is listed in Table 1.

3 | METHODOLOGY

3.1 | Discussion group

This report was prepared by the QA working group of the Varian Flash Forward Consortium (FFC). The working group was initiated by the FFC with the aim to develop a consensus document on how to perform machine QA of UHDR scanning proton beams enabling future patient treatment with FLASH transmission treatment plans.

The working group consisted of medical physicists from various proton therapy centers, all users of the Varian ProBeam system (Varian, a Siemens Healthineers Company, Palo Alto, USA). Most centers have a 250 MeV UHDR proton beam available in research mode, one center has used their UHDR proton beam on a group of patients within the FAST-01[6] and ongoing FAST-02 trials under a United States Food and Drug Administration

TABLE 1 Overview of definitions.

Cyclotron current	Indirect measure of number or protons per unit time produced by the cyclotron
Nozzle current	Indirect measure of number or protons per unit time passing through the ionization chamber in the nozzle
Spot dose [Gy]	Maximum dose at the center of a single spot assuming a Gaussian dose distribution in a given depth.
(Spot) dose rate [Gy/min]	Spot dose per unit time
Local dose rate	Dose rate at a given point calculated from the accumulated dose divided by the effective irradiation time corresponding to the same point considering a threshold dose value[15]
Adapted dose rate	The maximum dose rate of a measurement detector avoiding saturation effects
d, w, m, y	QA task frequency, being daily, weekly, monthly and yearly respectively
EPOM	Effective point of measurement
PDD	Percentage depth dose
Vertical deflector	An electrostatic component used to modulate the proton beam current output of the accelerator

(FDA) investigational device exemption (IDE). It should be stated that current experience is limited, therefore the conclusions of this working group are mainly based on discussions and opinions from field experts and partly based on experimental data.

3.2 | Process

In 2021, a risk assessment was performed with the aim of understanding what risks are involved in UHDR proton therapy to provide guidance on setting up a QA program to facilitate treatment with UHDR continuous proton beams in transmission mode. The premortem methodology proposed by Klein in 2007[16] was selected to perform a risk assessment. It is suggested to use this methodology before starting any new project. It is characterized by initiating a project group brainstorm session to identify and write down risks for the project by imagining the project has failed already, even before the project itself has started, thereby addressing the issues of overconfidence and optimism. To streamline further group discussions, all risks were grouped into categories and subcategories.

For conventional proton therapy, the AAPM report TG224[8] is widely used, and so was taken as a basis from which to adapt and add the required QA procedures for UHDR scanning proton beams. For each section, a discussion group of up to nine medical physicists met to discuss and share experience, and these discussion sessions were used to generate the current report.

To minimize overlap between the AAPM TG-224 report, the report presented here focuses only on proton beam specific QA, meaning that machine parameters, for example, table motion accuracy, are excluded and should be performed in accordance with the AAPM TG-224 report. In parallel, the FFC working group on dosimetry has been working on an overview of commercially available detectors and their behavior in a high-dose rate proton beam of which the results will be published in the future.

3.3 | Characteristics of an UHDR proton scanning beam

There are various commercial systems available that have the potential or are capable to deliver UHDR scanning proton beams. Before discussing QA procedures it is important to evaluate the technical capabilities, both similarities and differences, of these systems.

The isochronous cyclotron of a VARIAN ProBeam system delivers a 250 MeV quasi-continuous proton beam of up to a current of 800 nA at a frequency of 72 MHz. A beam transportation efficiency of ~50% from cyclotron to gantry can be achieved by fully retracting the beam energy degraders resulting in a UHDR proton beam with nozzle currents of up to ~400 nA. To ensure beam stability, the maximum nozzle current for the ProBeam system has been set to 215 nA by the vendor, corresponding to a cyclotron output current of ~450 nA. The nozzle's delivery system can scan a maximum field size of 30×40 cm^2 using scanning speeds of 5 and 20 m/s in crossline (x) and inline (y) directions, respectively. For a continuously scanning beam with a nozzle current of 215 nA, the system can deliver a 5×5 cm^2 field of 10 Gy uniform dose in about 280 ms using 5 mm spot spacing. Due to the nature of scanning beam delivery, larger field sizes prolong the total beam-on time.

For the IBA Proteus Plus multiroom systems, an IBA C230 isochronous cyclotron is used (IBA, Louvain-La-Neuve, Belgium), the system can deliver a maximum beam energy of 230 MeV at a maximum cyclotron current of 300 nA. With a beam transportation efficiency of ~60%, the maximum nozzle current lies at ~180 nA.[17] This value is similar to the ProBeam's nozzle current of 215 nA. The key difference between both systems is that the beam delivery is continuous for the ProBeam system, meaning that dose is also deposited between two consecutive spot positions, while the Proteus Plus performs a spot-by-spot delivery, which might affect the required QA at certain points of the QA program.

Mevion's Hyperscan (Mevion Medical Systems, Littleton, Massachusetts, USA) is another commercial

system capable of delivering scanning proton beams and has also been tuned to perform UHDR deliveries at the maximum beam energy of 230 MeV using a synchrocyclotron.[18,19] Also IBA has developed a synchrocyclotron, IBA S2C2, which is installed in the more compact IBA Proteus One (IBA, Louvain-La-Neuve, Belgium). Synchrocyclotrons produce pulsed beams for which the peak intensity can be in the order of μAs, however the average current is in the order of tens of nAs. This report focusses on isochronous cyclotrons producing a quasi-continuous beam such as the Varian ProBeam system and the IBA Proteus Plus system. Although part of the consensus on the QA procedures may also apply to synchrocyclotron systems, these systems were not included in this paper, as they fall outside the expertise of the working group.

3.4 | Scope of the work

The use of transmission proton beams for commissioned machines is assumed in this report, since they are more readily available and most short-term clinical applications are envisioned to use this approach. These beams are characterized by the absence of energy modulators resulting in high energy proton beams for which the Bragg peak lies beyond the patient, meaning only the plateau region of the depth dose profile resides in the patient, used for patient treatment. In addition, it is also assumed that an appropriate monitor chamber at the nozzle is installed that does not suffer from saturation effects at high dose rates.

Recently, extensive research has been conducted to prove the concept of Bragg peak FLASH, for example, using ridge filters and range shifters,[7] however, this is outside of the scope of this report. Despite the differences between transmission and Bragg peak FLASH, a similar QA program is expected where additional tests are envisioned for the latter, taking into account the specific end solution for Bragg peak FLASH.

3.5 | General beam settings and QA fields

Throughout this report, unless specified otherwise, some general machine settings are assumed to be as follows. First, a maximum beam energy of 250 MeV is intended for all tests. Second, the dose rate is the maximum dose rate for a specific plan maximized at a nozzle current of 215 nA. If other energies or dose rates are used, caution should be taken in interpreting the content of this report.

Clinically relevant dose rates are preferred for machine QA, however, for QA procedures an adapted (lower) dose rate may be required depending on the detector suitability for high dose rates, or, to limit activation when a long measurement time is required and dose rate is considered to be not relevant, for example, percentage depth dose (PDD) measurements.

To facilitate the QA procedures, a variety of standard QA fields are suggested ranging from a single spot up to fields composed of multiple spots (spot pattern). For example, a 3×3 cm^2 QA field consists of a spot pattern of equal dimensions meaning that the outer spot positions are 3 cm apart. All fields are centered on the central beam axis and the dose is defined on the central beam axis at the effective point of measurement (EPOM) of the detector. All composed QA fields have a dose of 10 or 20 Gy in combination with a spot pattern of 3×3, 5×5, 10×10 or 20×20 cm^2. A 5 mm spot spacing seems to be a reasonable value to create a homogeneous dose, however, this depends greatly on the size of a single spot.

With current treatment planning systems, it is not always possible to specify dose rate for treatment delivery. For the Varian ProBeam system, the dose rate depends on the lowest weighted spot. Because of this, the dose rate of spots in a field can effectively be reduced by adding a lower weighted spot. Where this is used, this spot should be positioned at least 5 cm out of field to minimize its dose contribution to the results of QA being performed. Note that it is not possible to increase the dose rate with this method adding a higher MU spot out of field.

3.6 | Guide to the reader

Section 4 discusses the results of the risk assessment. QA procedure are discussed in the subsequent Sections 5–9. All QA procedures originate from either the AAPM TG-224 report or the risk assessment performed by this group. In Sections 5 and 6, the origin of the QA procedure is marked at the beginning of each procedure by either "Risk assessment" or the corresponding AAPM TG-224 chapter(s). For the other sections, all QA procedures originate from the AAPM TG-224, it was decided to not specifically mark the origin of these QA procedures at these sections. In this report, only QA procedures that are different from the original AAPM TG-224 report are discussed.

Despite this report being created by a ProBeam user group, most QA procedures will also apply for other commercial or non-commercial isochronous cyclotron-based systems including those with spot-by-spot delivery. However, any anticipated differences in the QA procedure between continuous and spot-by-spot delivery have been identified, and an adapted QA procedure is proposed for spot-by-spot delivery.

4 | RISK ASSESSMENT

A premortem risk assessment exercise was conducted to identify risks that could lead to mistreatment of a

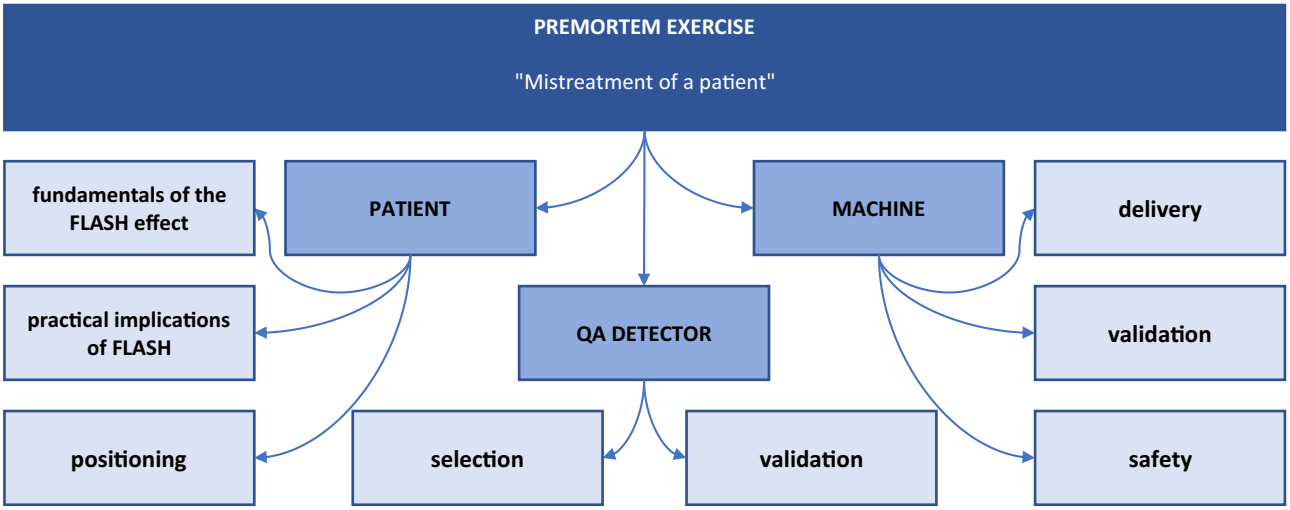

FIGURE 1 Overview of identified risk categories and subcategories, each sub category contains several risks that should be considered when performing UHDR proton therapy.

patient undergoing UHDR proton therapy. In total, 30 independent risks were identified which were grouped into several categories and subcategories (Figure 1). In the following paragraphs, we discuss the risks per subcategory and provide the rationale for why certain risks are or are not addressed in this report.

4.1 | Patient

Patient—fundamentals of the FLASH effect: Despite several research groups having demonstrated the presence of the FLASH effect in in vitro and animal studies, little is known about its application in humans or whether different tissue types require different beam delivery conditions. Therefore, the risk of UHDR treatment applied to a human patient is that the selected beam delivery characteristics for a given treatment site does not match the required criteria to induce the desired FLASH effect. Even in those cases in which the FLASH effect would be achieved, it may only hold up for early and not for long-term toxicity. If so, care should be taken when using the assumed wider therapeutic window of UHDR to treat more aggressively the tumor. Another aspect is that it is currently unknown what the impact of UHDR is on the RBE of transmission beams and how it differs from clinically used intensity-modulated proton therapy. For all identified risks pre-clinical research is required, and this falls outside the scope of this consensus on machine QA.

4.1.1 | Patient—practical implications of the FLASH effect

Most experiments to date, including the FAST-01 trial, have been based on single beam and single fraction delivery of at least 8 Gy per fraction and a minimum local dose rate of 40 Gy/s. However, future treatment schemes are likely to be fractionated with the potential use of multiple beams per fraction. In these latter scenarios, there is still much to understand about the dose and dose rate thresholds per beam and per fraction required to reach the desired FLASH effect, which could potentially lead to mistreatment. Another practical question is how to handle partial treatments, including beam interrupts, missing (partial) beams or fractions. These questions require further pre-clinical research and are considered beyond the scope of this report.

4.1.2 | Patient—positioning

Two patient positioning risks were identified: one patient-induced risk in the form of patient motion during treatment, and one treatment setup-induced risk, that is, misalignment of the patient on the treatment couch. Patient motion could be subdivided into expected and unexpected. The unexpected motion could be tackled by conventional methods such as patient monitoring via a live view camera. For the expected motion such as breathing the use of a gating system can be suggested, and this will be addressed in Section 7. Regarding patient alignment errors, it is important to establish proper image guidance protocols to assure correct patient alignment; however, this topic will not be further discussed.

4.2 | Machine

4.2.1 | Machine—delivery

UHDR radiotherapy comes with specific machine constraints. An important aspect of the Varian ProBeam system is that the minimum spot duration for a single

spot should be at least 2–3 ms, meaning that when a 215 nA nozzle current is used, the maximum dose per spot is approximately 4 Gy. In cases where a spot pattern with similar dose is required, the partly overlap of neighboring spots will force the nozzle current to be lowered to respect the minimal spot duration, resulting in a lower local dose rate achieved. Failure to be aware of these limitations may result in sub-optimal treatment plans. This risk can be mitigated through proper training. Since this is considered outside the scope of this report, no further attention is given to this topic. Another risk is that with high-speed delivery the delivered dose or dose rate is not accurate. This inaccuracy could be attributed to unexpected behavior of the monitor chamber, including dose non-linearity effects, and monitor chamber end or saturation effects. Furthermore, it is known from the ProBeam system that nozzle fluctuations of ±10 % are not uncommon, making it necessary to subject them to QA. These aspects are taken into account in Sections 5.1 and 5.3.

4.2.2 | Machine—safety

Currently, the Varian ProBeam UHDR proton beam is only available as a research tool and configured as an independent system for that reason. A switch of the system configuration is required to go from clinical mode to research mode and vice versa. Such an approach means that there is a risk that this switch is not carried out correctly. To mitigate this risk, a short test to verify some basic beam parameters such as dose, dose rate, energy and spot placement is essential. These tests will be addressed in several sections of Section 5. It is most likely that this issue will be solved in the future incorporation of UHDR into the clinical configuration. However, some basic tests will still be required.

4.2.3 | Machine—validation

Various aspects of machine behavior were addressed as risks. First, the time characteristics of the treatment delivery should be understood to avoid or minimize any negative impact on the desired FLASH effect. This underlines the importance of properly characterizing the UHDR proton beam. It is also important to monitor the machine behavior throughout its life span through a machine QA program. This is main focus of this report, including not only dose and geometry aspects, but also temporal dosimetry, which is the key difference between conventional and FLASH radiotherapy. A relative new development for the Varian ProBeam is the ability to use logfiles to verify beam delivery. In cases where this is employed, it is important to provide training on how to interpret the logfiles and validate their accuracy. The use of log files is left out of scope of this report but will be revisited in the discussion (Section 10).

4.3 | Detector

4.3.1 | Detector—selection

Several risks were identified regarding detector selection. First, with the introduction of the FLASH effect, the temporal behavior of the beam delivery has become more important compared to conventional radiotherapy. Most of the available commercial detectors were not developed with a focus on temporal dosimetry. Second, not all radiotherapy detectors function well at ultra-high dose rates, for example, due to saturation effects. Both of these risks emphasize the importance of careful detector selection, as an unsuitable detector could lead to mistreatment. This report aims to provide guidance on detector selection for specific QA procedures. Thirdly, in selecting the proper detector, it is also important to avoid relying on a single detector, meaning that each beam parameter should ideally be measured with two independent detectors. Another aspect considered is that the QA program performed should be time and cost-effective, meaning that the number of QA procedures and the duration of the total QA program should be designed in such a way that it is in balance with the frequency and severity of the risks. All off the previously mentioned points were taken into account when setting up this report.

4.3.2 | Detector—validation

Before using any detector for QA purposes, it is imperative to validate its performance. This includes validation of the proper functioning of the detector within the clinically used range of UHDR proton beams, encompassing beam intensity, dose, and dose rate. Furthermore, if relevant, special attention should be given to finding proper calibration factors.

Certain QA procedures involve specific phantoms, which should receive the same attention as the detector itself regarding selection and validation.

Despite its importance, validation of detectors was considered to be out of scope of this report.

5 | DOSIMETRY

5.1 | Absolute dosimetry

5.1.1 | Dose per monitor unit (D/MU)

Includes following procedures of AAPM TG 224: Dose per monitor unit (d) 2.A.1 / Dose per monitor unit (m) 4.A.1 / Dose per monitor unit (y) 5.A.1

Dose per monitor unit (y): Reference dosimetry should be performed in accordance with IAEA TRS-398 report[20] using an ionization chamber in water.

Measurement setup: Align the water phantom and detector in line with the local reference conditions for

output measurements. Deliver a spot pattern of at least 5×5 cm^2 and a dose of 10 Gy to the effective point of measurement (EPOM) of the ion chamber. Dose per MU linearity will be discussed in Section 5.1.2, which for ultra-high dose rates also includes linearity for various dose rates to assure a correct dose delivery in this range.

Detectors: Advanced Markus (PTW, Freiburg, Germany) and PPC05 (IBA, Louvain-La-Neuve, Belgium)

Limits: ± 1% dose difference

Dose per monitor unit (m): For the monthly output measurement a measurement in solid water should be sufficient using an ionization chamber cross-calibrated with the yearly output measurement.

Measurement setup: Use the same measurements setup as for the yearly QA. Deliver a 5×5 cm^2 QA field with a dose of 10 Gy to the EPOM of the ion chamber. Preferably, the QA plans of the monthly and yearly output measurements are the same with similar dose rate.

Detectors: Advanced Markus and PPC05

Limits: ± 2%

Dose per monitor unit (d): An output constancy check should be sufficient for a daily output check using a dedicated daily QA device.

Measurement setup: For a consistency check it is possible to deviate from the reference conditions regarding the measurement setup. The use of the 5×5 cm^2 field and a dose of 10 Gy to the EPOM of the detector is preferred.

Detectors: A dedicated daily QA device would be the preferred option, however, none of the commercial systems have been validated. Therefore, the monthly QA setup is proposed as an alternative.

Limits: ± 3%

5.1.2 | Monitor chamber linearity, reproducibility, and min/max checks

Includes following procedures of AAPM TG 224: Monitor chamber linearity, reproducibility, and min/max checks (y) 5.A.9

Linearity and reproducibility (y): A linearity response of the nozzle's monitor chamber should be checked on an annual basis taking into account both variation in monitor units (MU) per spot and variations in dose rate. The latter is especially important since it is the link between all machine QA measurements performed with a large spread of dose rates. For machine QA, the highest possible dose rates are desired from a clinical perspective. However, the opposite is true for PDD measurements to limit activation levels. In addition, not all field detectors are able to function at maximum dose rate.

Measurement setup: Deliver a single spot to a Faraday cup aligned to the isocenter. This measurement should be repeated for various MU per spot and dose rates covering a suitable range of values that is representative for clinic and QA. Apply 5 different MU per spot and 5 different dose rates (each equally spaced over the relevant range) for a total of 25 measurements.

Detectors: BC-75 Faraday cup (Pyramid, Waltham, USA). If a Faraday cup is unavailable an Advanced Markus or PPC05 could be used, however, a treatment field (e.g., 3×3 cm^2 spot pattern) instead of a single spot should be used to avoid partial volume effects.

Limits: 1%

5.1.3 | Monitor chamber end effect

Includes following procedures of AAPM TG 224: Monitor chamber end effect (y) 5.A.10

Monitor chamber end effect (y): For each treatment plan the number of MU per spot is specified to deliver some required dose. These MU are related to the signal recorded by the monitor chamber in the nozzle which is used to stop the dose delivery once the requested number of MU has been delivered. However, there is always a delay between signal detection, when the requested number of MU is reached, and stopping the beam. A method of testing the monitor chamber end effect is to request and deliver a number of MU in a single delivery and repeat by splitting up over multiple lower MU deliveries summing to the same total MU. Ideally, both deliveries should give the same output within a small deviation.

Measurement setup: Align a Faraday cup to the isocenter and deliver a single spot serving as a reference. Second, deliver the same total number of MU, however, this time fractionated within a single measurement. The latter need to be done for three equally divided lower MU-weighted spots, resulting in three beam deliveries in a single measurement. Compare both readings to determine the monitor chamber end effect. This test needs to be repeated for five equidistant levels of MU covering the full range of MU per spot considered to be clinically relevant. Make sure to also include the minimal allowable MU weight into the QA procedure, since in this region of MU weights the monitor chamber end effect is expected to be most prominent.

Detectors; BC-75 Faraday cup, if not available also a PTW Advanced Markus or IBA PPC05 could be used but again use a field instead to avoid the partial volume effect.

Limits: The summed dose of the fractionated fields should be within 1% dose reading with respect to the reference.

5.2 | Relative dosimetry

5.2.1 | Range

Includes following procedures of AAPM TG 224: Range (d) 2.A.2 / Range (m) 4.A.2 / Range (y) 5.A.2 / Integral depth-dose distribution (y) 5.A.5

Range (y): The range of a pristine Bragg peak in water should be determined annually by performing a PDD

measurement. PDD measurements can be acquired at gantry angle 0° or 90°. There are pros and cons for both gantry angles. At gantry angle 0°, it is possible to measure up to the water surface. Care should be taken with such measurements to minimize disturbing of the water surface as the detector is moved through the water. For that reason, it is preferred to move the detector from bottom to top, also appropriate delay times should be used to minimize the effect. Water surface effects can also be avoided by using a gantry angle of 90°, however, near surface measurements are not possible due to the presence of the water tank wall. In addition, the stopping power of the water tank wall differs from water and therefore has to be taken into account.

Measurement setup: large water phantom with the beam entry surface aligned to isocenter, gantry at 0° or 90°. Reference detector positioned outside of the water phantom (in front of beam) and the field detector in water. Perform a measurement along the central beam axis of a continuous single spot at an adapted dose rate to limit the activation and to avoid detector saturation effects.

Detectors; Bragg Peak chamber (PTW, Freiburg, Germany) or Stingray (IBA, Louvain-La-Neuve, Belgium) could be used as field detector and a reference detector; X-ray Therapy monitor chamber [large size plane parallel transmission chamber] (PTW, Freiburg, Germany).

Limits: ± 1 mm for distal 80% depth dose

Range (m):

Measurement setup: a multi-layer ionization chambers (MLIC) detector is aligned to the isocenter to detect the PDD of a single spot. Where the maximum energy for the selected detector is exceeded, it is recommended to position a stack of solid water slabs (the water equivalent thickness is needed) in front of the detector to pull back the Bragg peak into the detection range of the detector. It is important to note that current commercial MLIC detectors are vulnerable to saturation effect, therefore an adapted dose rate is proposed. An alternative method would be the use of a flat scintillation screen in combination with a wedged phantom, which are dose rate independent but are more difficult to interpret.

Detectors: Giraffe (IBA, Louvain-La-Neuve, Belgium), Zebra (IBA, Louvain-La-Neuve, Belgium), or XRV3000 Eagle (Logos Systems, Scotts Valley, USA) or XRV4000 Hawk (Logos Systems, Scotts Valley, USA) in combination with a Ranger-300 (Logos Systems, Scotts Valley, USA). For the latter minor modifications are necessary to reduce the net range in the detector by adding slabs in between the beam and the Ranger-300.

Limits: ± 1 mm for distal 80% depth dose

Range (d): Most dedicated daily QA devices have an option to validate beam energy by creating various water equivalent path lengths within the device before reaching the EPOM of the detector. By adding pillars of materials on top of the phantom the effective path lengths can be optimized to measure at least 2 points,[21] one in between the distal 80% and 20% depth dose and one at or near (on the proximal side) the proximal 90% isodose of any given pencil beam.

Measurement setup: Align the detector to the isocenter and deliver a spot pattern onto the detector, at least two points in the distal penumbra must be measured using the variety of effective path lengths.

Detectors: The use of daily QA devices would be the preferred option. However, these have not yet been validated. An adapted dose rate might be needed to perform this measurement. If not, the suggestion is to use the measurement setup of the monthly QA.

Limits: ± 1 mm for the selected points on the PDD curve.

5.2.2 | Spot position and shape

Includes following procedures of AAPM TG 224: Spot delivery constancy (d) 2.A.4 / Spot angular-spatial distribution and lateral dose profiles (y) 5.A.6 / Spot position (y) 5.A.7

Spot angular-spatial distribution and lateral dose profiles (y): The dose distribution of a single spot has a large influence on an optimized dose distribution and should therefore be well modeled in the treatment planning system. This means that the spot profile should be verified periodically for different gantry angles and a variety of source surface (detector surface) distances near the isocenter.

Measurement setup: A 2D detector with a high spatial resolution should be used to perform relative dose measurements in air for a single spot on the central beam axis. As a minimum, the following gantry angles should be covered: 0°, 90°, 180° (if feasible), and 270° combined with at least three source-to-surface distance (isocenter and isocenter ± 10 cm). For each measurement, the spot sigma should be determined and compared to the commissioning data.

Detectors: Gafchromic film, Lynx PT (IBA, Louvain-La-Neuve, Belgium), XRV4000 Hawk, and XRV3000 Eagle (Logos Systems, Scotts Valley, USA).

Limits: ±10% difference in spot sigma.

Spot position (y): Each delivered spot that deviates from the central beam axis is steered by the steering magnets toward the requested spot position. It is important to verify at least once a year if the steering magnets are functioning properly for different gantry angles.

Measurement setup: align a 2D detector to the isocenter and perform a relative integrated dose measurement of a grid consisting of well separated single spots, including a spot on the central axis. The spot pattern should ideally cover the maximum field size with a spot spacing of 3–5 cm, the latter is to make sure that dose contributions of neighboring spots is minimized since

integrated dose measurements are performed. The test should be repeated for at least the following four gantry angles: 0°, 90°, 180° (if feasible), and 270°.

Detectors: Gafchromic film or a scintillation-based system such as the Lynx PT (IBA, Louvain-La-Neuve, Belgium), XRV4000 Hawk, or XRV3000 Eagle (Logos Systems, Scotts Valley, USA).

Limits: 0.5 mm relative position, 1 mm absolute position.

Spot delivery constancy (d): a daily spot pattern should be checked for positioning and lateral dose distribution. This could be a series of single standalone spots or a composed treatment field. In all cases the positioning and spot shape or lateral penumbra should be verified.

Measurement setup: position a 2D detector at the isocenter delivering a spot pattern. The outer positions of the selected spot pattern should at least cover an area of 10×10 cm^2.

Detectors: Although a dedicated daily QA device is preferred it has not yet been validated therefore an alternative detector should be used, for example, Gafchromic film, 1600XDR (PTW, Freiburg, Germany, system has an upper limit of recordable dose in the order of 10 Gy) or a strip ionization chamber[11]

Limits: 2 mm/1 mm for absolute/relative positioning. 2 mm for the lateral dose distribution.

5.2.3 | Flatness and symmetry of broad fields

Includes following procedures of AAPM TG 224: Flatness and symmetry of broad fields (m) 4.A.3

Flatness and symmetry of broad fields (m): Verification of composed treatment fields is considered important since it mimics more closely an actual patient treatment field compared to single spots. However, the flatness and symmetry parameters are considered inappropriate since it was defined for a passive scatter beam using only three measurement points: dose on central beam axis and two lateral in-field positions. Instead, the use of uniformity is considered more relevant since it takes into account all measurement points and is therefore proposed.

Measurement setup: a 2D detector for relative or absolute dose measurements is aligned to the isocenter. A mono energetic spot pattern of at least 10×10 cm^2 delivering a dose of 10 Gy to the EPOM for various gantry angles, being at least: 0°, 90°, 180° (if feasible), and 270°. Perform a gamma evaluation comparing the dose measurement with a reference dose distribution from the treatment planning system.

Detectors: Gafchromic film or 1600XDR

Limits: a gamma passing rate of $\geq 90\%$ using gamma criteria 2 mm/2%

5.3 | Temporal dosimetry

5.3.1 | Dose rate and dose rate constancy

Risk assessment

Dose rate and dose rate constancy (y): During spot scanning a constant dose rate is paramount to uphold the planned local dose rate. As all the spots in a planned field will be delivered using the same dose rate, it is more efficient and statistically valuable to measure a complete treatment field than repeating single spot measurement for a dose rate and dose rate constancy check. Dose rate is defined as the maximum dose of a spot's dose distribution per unit time, it is recommended to determine the integrated dose per unit time as indirect measure of dose rate under the assumption that the spot shape stays constant.

Measurement setup: align the detector to isocenter and measure the dose delivery in time for various scan patterns, spatial information is not a must for this test. At least three spot patterns with various dimensions for two different dose levels are recommended. Make sure that the outer limits of what is considered clinically relevant are included, for example, 3×3 cm^2, 5×5 cm^2 and 10×10 cm^2 in combination with the following dose levels, for example, 10 and 20 Gy. For each treatment plan the dose delivery over time is monitored

Detectors: a large surface high temporal resolution detector is required, for example, strip ionization chamber, large Faraday cup.

Limits: The dose rate constancy may vary significantly from day to day and from center to center and it depends on the cyclotron's stability. This is not an UHDR specific issue and is also true for conventional proton therapy though there it is less significant. Since experimental data is lacking, the limit for this measurement should be customized by individual institutions. It is important that each center familiarizes itself with their cyclotron behavior and the limit is then selected in such a way that a minimum dose rate can be assured for FLASH treatment delivery.

In the case of spot-by-spot delivery, it is expected that the proposed QA procedure will lead to an underestimation of the nozzle current due to planned beam interruptions in between each spot position. For that reason, it is proposed to use a single pencil beam instead of a spot pattern. The weight of the single spot should be equal to the total weight of the spot pattern.

Dose rate (m):

Measurement setup: A similar strategy is applied for the monthly QA with respect to the yearly QA. Only a single spot patterns of intermediate dimensions and dose, for example, 5×5 cm^2 and 10 Gy, is delivered onto a detector aligned to the isocenter.

Detectors: a large surface detector with a high temporal resolution is required, for example, a strip ionization

chamber or a large faraday cup. The BC-75 faraday cup could be used although the allowable field size is limited due to the limited sensitive area of the detector.

Limits: use the same limit for yearly QA on dose rate

In the case of spot-by-spot delivery, the same transformation from spot pattern to single spot can be used, as described for the doserate (y).

Dose rate (d):

Measurement setup: For daily QA it should be sufficient to determine only the total beam delivery time for a spot pattern, assuming the delivered integrated dose is constant.

Detectors: any 2D QA device able to perform a relative or absolute dose measurement in time with a high temporal resolution, the latter should be at ≤1% of the total treatment delivery time. For example, if the expected delivery time is 500 ms, then a temporal resolution of 5 ms is required. By changing plan parameters one can tune the treatment plan to match the measurement device.

Limits: Use the same limit for yearly QA on dose rate

5.3.2 | Dose spillage

Risk assessment

Dose spillage (y): Using a continuous proton beam, the time to move from one spot to the next will result in dose delivery in between spots which we term as spillage. Current systems are able to temporarily stop the beam in between two spot positions using the vertical deflector. However, this results in a lower local dose rate. Although treatment planning systems do not take into account spillage there is a need to determine its magnitude. In essence spillage is also verified during measurement-based patient and machine QA. Therefore, a yearly verification should suffice.

Measurement setup: determine spillage of dose during plan delivery by delivering the same treatment plan twice, one time irradiated with a continuous beam and one time irradiated with a beam that stops in between. For the Varian Probeam system, it is possible to enable or disable the use of the vertical deflector in between spot positions. The dose difference between both dose distributions will give information about the impact of dose spillage.

Align a 2D detector at the isocenter and deliver several QA plans using a variety of spot patterns (3×3, 5×5, and 10×10 cm^2) and various values of MU per spot. Make sure to use at least four equidistant MU levels including the minimum and maximum MU per spot used in the clinic. One time with continuous beam (raster mode/smearing mode) and one time without continuous beam (spot mode) by activating the vertical deflector in between spot positions. Perform a gamma evaluation between the two dose measurements for each QA plan.

Detectors: 2D dose detector like Gafchromic film, strip ionization chamber or 1600XDR

Limit: gamma criteria 1% and 1 mm, gamma index should be ≥90%.

In the case of spot-by-spot delivery, dose spillage is a continuous beam delivery-specific feature and does not play a role. Therefore, it is not necessary to perform this test for systems that employ this delivery technique.

5.3.3 | Scanning speed

Risk assessment

To maintain the FLASH effect in a scanning proton beam, not only a high dose rate of the pencil beam itself is required, but also fast delivery over the target is paramount. Scanning speeds differ depending on the scanning direction X (lateral) or Y (table to gantry).

Scanning speed (y): An in-depth verification is proposed using detectors with sub-millisecond accuracy, assuming a minimum of approximately 3 ms per spot delivery. A spatial resolution of at least 3 mm is assumed to be good enough to properly determine spot position.

Measurement setup: Position a 2D detector at isocenter. The following QA treatment fields of clinically relevant size and dose are required: spot patterns of 3×3, 5×5, and 10×10 cm^2 with the following combinations of dose: 10 and 20 Gy. The detector will produce independent dose frames from which the spot position can be obtained, meaning it is possible to separate the traveling spots from the static spots. Knowing the spot spacing and the time in between spots the scanning speed for X and Y direction can be obtained.

Detectors: a strip ionization chamber with high temporal resolution (repetition rate of ≤ 0.1 ms).

Limits: Currently, the proper limit is unknown, therefore the proposition is to evaluate machine behavior and set limits according to what is acceptable for your current clinical practice.

In the case of spot-by-spot delivery, scanning speed, or the time that the steering magnets need to reach the new spot position, cannot be monitored when the beam is stopped in between two spot position. Nevertheless, to maintain a high local dose rate, it is essential for spot-by-spot delivery systems to have a fast and predictable scanning speed. An alternative method is to determine the time needed to go from one spot position to the next.

Scanning speed (m):

Measurement setup: A standard QA treatment field should be measured, preferably one of the yearly QA plans is selected to have a proper reference. Setup and analysis is similar to the yearly QA procedure.

Detectors; strip ionization chamber with high temporal resolution.

Limits: See limit of yearly scan speed QA

In the case of spot-by-spot delivery, the proposed procedure for scanning speed (y) can also be applied for scanning speed (m).

6 | MECHANICAL

6.1 | Gantry isocentricity and coincidence of proton- and imaging-isocenter

Includes following procedures of AAPM TG 224: Gantry and couch isocentricity (m) 4.B.1 / Coincidence of x-rays, light field, and proton radiation field (m) 4.B.4

Within the AAPM TG-224 report, gantry isocentricity and coincidence of the proton field with the x-ray imager isocenter are highlighted as separate parameters, however, both parameters could be evaluated within a single measurement setup.

Measurement setup: position a 2D scintillation detector at isocenter using the orthogonal lasers. Perform imaging according to clinical protocol, for example, gantry 45° to obtain kV images from AP and LAT, to position the detector at the imaging isocenter. Deliver a single spot for at least eight equidistant gantry angles covering the full range of gantry angles. The reading from the scintillation screen contains information about the spot position with respect to the imaging isocenter.

Detectors: XRV-100 and XRV-124 (Logos Systems, Scotts Valley, USA)

Limit: a limit of $\leq$ 1.5 mm is expected to be achievable.

7 | PATIENT MONITORING

7.1 | Imaging

No difference is foreseen in the imaging QA program comparing UHDR beams with conventional proton beams. However, there is a minor concern that due to FLASH treatments the delivered dose per unit time will increase degradation of the imaging panels. For this reason, it might be beneficial to perform QA on image quality more frequently.

7.2 | Gating

A correct timing of UHDR beam delivery in case of moving target is paramount to assure an adequate treatment. Therefore, the use of gating techniques is proposed by[22] to achieve gated or deep inspiration breath hold (DIBH) treatments. In general, there are two gating techniques currently available for clinical use in proton therapy: 1) the use of non-spirometric external surrogates such as the Real-time Position Management (RPM) and Respiratory Gating for Scanners (RGSC) systems from Varian (Varian Medical Systems, Palo Alto, USA) and surface guided radiation therapy (SGRT) using AlignRT (VisionRT Ltd. London, UK), and 2) use of spirometric techniques to obtain a surrogate for internal lung volume and tidal air flow such as Active Breathing Coordinator (ABC: Elekta, Stockholm, Sweden) and SDX (Dyn'R, Toulouse, France). Generally, the functionality of gating systems should be tested and dosimetric evaluation should be performed. The functionality (or safety) test needs to be done to assess the beam triggering, both beam-on and beam-off, based on the gating system's signal. Please note that the aim should be to deliver the full fraction dose within a single gating window so as not to lose any potential FLASH effect. Typically, the gated systems have a delay in the order of milliseconds up to a second to send the signal to the delivery system (proton machine) in order to check the stability of the surrogate (spirometric or non-spirometric) signal. Therefore, it is important to take these delays into account when setting the desired gating window. The purpose of the dosimetric validation is to evaluate the detector measurements with gating (dynamic) and without gating (static). To do that, one (or more) gated plan(s) should be used to validate the minimal dosimetric effect of gated delivery compared to a static measurement.

8 | SAFETY

For conventional proton beam therapy, the beam energy is modulated to deliver the Bragg peak in proximity of the target, meaning a majority of the pencil beams are absorbed completely by the patient. With transmission FLASH only the plateau of the Bragg peak will be used for patient treatment and as a result large part of the beam's energy is absorbed by a part of the gantry opposite to the nozzle. For a Varian ProBeam system this means that the counterweight will receive a significant amount of dose. The consensus is that not only the treatment room ambient dose due to activation should be monitored, but also the activation of the counterweight on a regular basis.

9 | INDEPENDENT AUDIT

Since reference dosimetry in UHDR beams is challenging and dose rate has become an important factor with the introduction of FLASH, an independent audit is considered paramount before starting patient treatment. To our knowledge, there is no dedicated audit service currently available. Until such a service is widely available, collaboration between proton centers and local metrology institutes to cross check each other on absolute dose and dose rate using their own independent dosimetry protocols is recommended.

10 | DISCUSSION

Gantry-based UHDR proton beams have only recently become technically available, opening up the potential of FLASH proton therapy. This means that the current machine QA procedures must be expanded to ensure that such UHDR deliveries are performed accurately and safely for both research and future clinical use. The main contribution of this report is that an international group of Varian ProBeam users with UHDR capability reached consensus on how machine QA for UHDR proton therapy could be performed based on the knowledge and data we have currently available. While this report was written by a group of VARIAN ProBeam users, it may also be applicable to systems of other vendors. However, caution should be exercised when interpreting this report for other systems. Note that we pointed out the differences in QA procedures with other isochronous cyclotron-based systems that use spot-by-spot delivery.

Currently, the AAPM TG-224 is considered to be the gold standard for machine QA for proton therapy. This report is set up as an extension of this standard for UHDR proton beams. Only proton-beam specific parameters were evaluated, as the only differences between conventional and UHDR proton therapy relate to the proton beam itself (e.g., table isocentricity and snout positioning accuracy are excluded). Some proton beam specific parameters were also excluded for the following reasons:

- *Range uniformity (y) 5.A.4* was not considered relevant since small fields are foreseen in patient treatment and in transmission mode the plateau region is used with the consequence that small variations in range have negligible impact on patient dosimetry.
- All parameters in relation to Spread Out Bragg Peak (SOBP) & relative range are omitted (*Includes following procedures of AAPM TG 224: SOBP width and relative range (d) 2.A.3 / SOBP width (y) 5.A.3*) since monoenergetic transmission beams are not actively modulated in depth.
- Transmission beams are not currently delivered using (multi-leaf) collimators and therefore adjacent machine parameters were excluded (*Includes following procedures of AAPM TG 224: MLC leakage (y) 5.A.12 / MLC activation (y) 5.A.13*).
- Dosimetry factors were omitted (*Includes following procedures of AAPM TG 224: Dosimetry factors (y) 5.A.11*) as they were only considered to be relevant for passive scattering proton beams.
- Finally, inverse-square correction tests (*Includes following procedures of AAPM TG 224: Inverse-square correction test (y) 5.A.8*) are part of the commissioning procedure and once determined are not expected to change since it is related to the gantry design and therefore not relevant to include in routine machine QA.

Commercial system that deliver a scanning proton beam can make use of an isochronous cyclotron or a synchrocyclotron. The FFC working group has no experience with the use of synchrocyclotrons and, therefore considered it out of scope for this report. However, in general, most of the concepts described in this report will also apply for synchrocyclotrons-based systems. The main challenge lies in finding the proper detectors for two reasons. First, the selected detector should not saturate at nozzle currents that can reach microamperes per pulse. Second, to be able to discriminate pulse durations, the temporal resolution of the detector should be in the order of microseconds.

The risk assessment has revealed some important aspects that should be considered before starting UHDR proton treatment. While several aspects have been addressed within this report, a number of aspects were considered out of the scope. The aspects out of scope can be used as starting point for further discussions related to the clinical implementation of UHDR radiotherapy.

It is important to emphasize that the existing literature on machine QA is currently limited. Therefore, we have sought the insights of firsthand users and field experts to gather their preliminary experiences and opinions. Further research is necessary to transform the current consensus and expert opinions into well-founded recommendations.

Developments in UHDR proton beam delivery systems suggest that the most likely step forward is Bragg peak FLASH after transmission FLASH. By applying beam modifiers such as ridge filters and range shifters close to the patient, the FLASH effect may be achieved for conformal dose distributions. However, at the time this report was prepared, the availability of and experience with this technique among the members of the consensus group was limited, so this topic was considered beyond the scope of this report, but will be part of future work of this group.

During the writing of this report, it also became clear that there is a lack of commercially available time resolved detectors with sufficiently high temporal resolution ($\leq$ 0.1 ms). It is a positive sign that the first publications considering one dimensional[13,14] and two dimensional detectors[11] have been published suggesting that solutions are being developed. In the absence of suitable detectors, the use of log files produced by the machine itself was proposed as an alternative solution. Even though log file based QA is considered to be a powerful tool to support or extend machine QA,[23] it was considered that it cannot currently replace an independent measurement. Moreover, it was challenging to determine suitable limits due to the limited availability of machine QA data of UHDR proton beams. Therefore, there is a clear need to collect and share machine QA results allowing future refinement of the suggested limits.

11 | CONCLUSION

Several discussion sessions amongst field experts resulted in an initial set of practical guidelines for machine QA for UHDR scanning proton beams in transmission mode for isochronous cyclotron-based systems. Consensus was reached regarding the parameters to be tested and methods for conducting these QA tests. Action limits were defined for most tests; however, for certain tests, limits could not be defined due to a lack of machine QA data specific to UHDR proton beams. In such cases, a strategy is proposed to determine these limits when more data becomes available. Additionally, there is a clear need for commercial detectors with high temporal resolution to facilitate temporal dosimetry.

ACKNOWLEDGMENTS

The authors thank Michael Folkerts, Tina Pfeiler, and Isabel Huth from Varian Medical Systems for their input during discussions and critical reading.

CONFLICT OF INTEREST STATEMENT

The working group received support from Varian, a Siemens Healthineers Company, within the Flash Forward Consortium (Varian, a Siemens Healthineers Company, Palo Alto, California, USA) to organize all meetings, no financial fundings were received.

REFERENCES

1. Favaudon V, Caplier L, Monceau V, et al. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med*. 2014;6(245). doi:10.1126/scitranslmed.3008973
2. Montay-Gruel P, Petersson K, Jaccard M, et al. Irradiation in a flash: unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s. *Radiother Oncol*. 2017;124(3):365-369. doi:10.1016/j.radonc.2017.05.003
3. Vozenin M-C, de Fornel P, Petersson K, et al. The advantage of FLASH radiotherapy confirmed in Mini-pig and Cat-cancer patients. *Clin Cancer Res*. 2019;25(1):35-42. doi:10.1158/1078-0432.CCR-17-3375
4. Bourhis J, Sozzi WJ, Jorge PG, et al. Treatment of a first patient with FLASH-radiotherapy. *Radiother Oncol*. 2019;139:18-22. doi:10.1016/j.radonc.2019.06.019
5. Gaide O, Herrera F, Jeanneret Sozzi W, et al. Comparison of ultra-high versus conventional dose rate radiotherapy in a patient with cutaneous lymphoma. *Radiother Oncol*. 2022;174:87-91. doi:10.1016/j.radonc.2021.12.045
6. Mascia AE, Daugherty EC, Zhang Y, et al. Proton FLASH radiotherapy for the treatment of symptomatic bone metastases. *JAMA Oncology*. 2023;9(1):62. doi:10.1001/jamaoncol.2022.5843
7. Simeonov Y, Weber U, Schuy C, et al. Monte Carlo simulations and dose measurements of 2D range-modulators for scanned particle therapy. *Zeitschrift Für Medizinische Physik*. 2021;31(2):203-214. doi:10.1016/j.zemedi.2020.06.008
8. Arjomandy B, Taylor P, Ainsley C, et al. AAPM task group 224: comprehensive proton therapy machine quality assurance. *Med Phys*. 2019;46(8):e678-e705. doi:10.1002/mp.13622
9. Petersson K, Jaccard M, Germond JF, et al. High dose-per-pulse electron beam dosimetry -A model to correct for the ion recombination in the advanced markus ionization chamber. *Med Phys*. 2017;44(3):1157-1167. doi:10.1002/mp.12111
10. McManus M, Romano F, Lee ND, et al. The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate very high energy electron beams. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-65819-y
11. Yang Y, Shi C, Chen C, et al. A 2D strip ionization chamber array with high spatiotemporal resolution for proton pencil beam scanning FLASH radiotherapy. *Med Phys*. 2022;49(8):5464-5475. doi:10.1002/mp.15706
12. Lee E, Lourenço AM, Speth J, et al. Ultrahigh dose rate pencil beam scanning proton dosimetry using ion chambers and a calorimeter in support of first in-human FLASH clinical trial. *Med Phys*. 2022;49(9):6171-6182. doi:10.1002/mp.15844
13. Verona Rinati G, Felici G, Galante F, et al. Application of a novel diamond detector for commissioning of FLASH radiotherapy electron beams. *Med Phys*. 2022;49(8):5513-5522. doi:10.1002/mp.15782
14. Marinelli M, Felici G, Galante F, et al. Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry. *Med Phys*. 2022;49(3):1902-1910. doi:10.1002/mp.15473
15. Folkerts MM, Abel E, Busold S, Perez JR, Krishnamurthi V, Ling CC. A framework for defining FLASH dose rate for pencil beam scanning. *Med Phys*. 2020;47(12):6396-6404. doi:10.1002/mp.14456
16. Klein G. Performing a project premortem. *Harv Bus Rev*. 2007.
17. Pidikiti R, Patel BC, Maynard MR, et al. Commissioning of the world's first compact pencil-beam scanning proton therapy system. *J Appl Clin Med Phys*. 2018;19(1):94-105. doi:10.1002/acm2.12225
18. Darafsheh A, Hao Y, Zwart T, et al. Feasibility of proton FLASH irradiation using a synchrocyclotron for preclinical studies. *Med Phys*. 2020;47(9):4348-4355. doi:10.1002/mp.14253
19. Darafsheh A, Hao Y, Zhao X, et al. Spread-out Bragg peak proton FLASH irradiation using a clinical synchrocyclotron: proof of concept and ion chamber characterization. *Med Phys*. 2021;48(8):4472-4484. doi:10.1002/mp.15021
20. Andreo P, Burns DT, Hohlfeld K, et al. IAEA TRS-398: Absorbed dose determination in external beam radiotherapy: an international code of practice for dosimetry based on standards of absorbed dose to water. 2006.
21. Ding X, Zheng Y, Zeidan O, et al. A novel daily QA system for proton therapy. *J Appl Clin Med Phys*. 2013;14(2):115-126. doi:10.1120/jacmp.v14i2.4058
22. Yang Y, Kang M, Huang S, et al. Impact of respiratory motion on proton pencil beam scanning FLASH radiotherapy: an in silico and phantom measurement study. *Phys Med Biol*. 2023;68(8):085008. doi:10.1088/1361-6560/acc632
23. Kanouta E, Johansen JG, Kertzscher G, Sitarz MK, Sørensen BS, Poulsen PR. Time structure of pencil beam scanning proton FLASH beams measured with scintillator detectors and compared with log files. *Med Phys*. 2022;49(3):1932-1943. doi:10.1002/mp.15486

How to cite this article: Spruijt K, Mossahebi S, Lin H, et al. Multi-institutional consensus on machine QA for isochronous cyclotron-based systems delivering ultra-high dose rate (FLASH) pencil beam scanning proton therapy in transmission mode. *Med Phys*. 2023;1-13. https://doi.org/10.1002/mp.16854