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Original Article

# Hybrid ultra-high and conventional dose rate treatments with electrons and photons for the clinical transfer of FLASH-RT to deep-seated targets: A treatment planning study

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ABSTRACT

*Purpose:* This study explores the dosimetric feasibility and plan quality of hybrid ultra-high dose rate (UHDR) electron and conventional dose rate (CDR) photon (HUC) radiotherapy for treating deep-seated tumours with FLASH-RT.

*Methods:* HUC treatment planning was conducted optimizing a broad UHDR electron beam (between 20–250 MeV) combined with a CDR VMAT for a glioblastoma, a pancreatic cancer, and a prostate cancer case. HUC plans were based on clinical prescription and fractionation schemes and compared against clinically delivered plans. Considering a HUC boost treatment for the glioblastoma consisting of a 15-Gy-single-fraction UHDR electron boost supplemented with VMAT, two scenarios for FLASH sparing were assessed using FLASH-modifying-factor-weighted doses.

*Results:* For all three patient cases, HUC treatment plans demonstrated comparable dosimetric quality to clinical plans, with similar PTV coverage ($V_{95\%}$ within 0.5 %), homogeneity, and critical OAR-sparing. At the same time, HUC plans delivered a substantial portion of the dose to the PTV ($D_{median}$ of 50–69 %) and surrounding tissues at UHDR. For the HUC boost treatment of the glioblastoma, the first FLASH sparing scenario showed a moderate FLASH sparing magnitude (10 % for $D_{2\%,PTV}$) for the 15-Gy UHDR electron boost, while the second scenario indicated a more substantial sparing of brain tissues inside and outside the PTV (32 % for $D_{2\%,PTV}$, 31 % for $D_{2\%,Brain}$).

*Conclusions:* From a planning perspective, HUC treatments represent a feasible approach for delivering dosimetrically conformal UHDR treatments, potentially mitigating technical challenges associated with delivering conformal FLASH-RT for deep-seated tumours. While further research is needed to optimize HUC fractionation and delivery schemes for specific patient cohorts, HUC treatments offer a promising avenue for the clinical transfer of FLASH-RT.

## Introduction

Doses delivered at ultra-high dose rates (UHDR, $\gtrsim$ 40 Gy/s) have the potential to improve the therapeutic index of radiotherapy (RT) by sparing normal tissues while retaining tumour toxicity compared to doses delivered at conventional dose rate (CDR, ~0.01–1 Gy/s) [1]. This phenomenon has been termed FLASH effect and was confirmed in an extended range of preclinical animal models by multiple institutions and for multiple particle species [1–4] (and references therein). So far, the FLASH effect was predominantly explored in preclinical and clinical settings using broad UHDR electron beams of 4–30 MeV [1–3,5–9]. These UHDR beams are suitable for treating superficial skin lesions and for intra-operative RT [10–16]. However, due to their limited ranges and large penumbrae, they do not allow to deliver a dosimetrically conformal treatment to deep-seated tumours ($\gtrsim$5 cm) on their own. The conformal treatment of such tumours at UHDR represents one of the major technical challenges for the clinical transfer of FLASH-RT and multiple UHDR treatment devices and beam types have been proposed

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to this end, including very-high energy electrons (VHEE, 50–250 MeV), photons, protons, and ions [17–20]. Recent experimental data suggests that all the dose of a UHDR treatment session needs to be delivered to normal tissues within a short overall time (~100 ms) and without pauses when delivering multiple beams for an optimized FLASH sparing effect [21–23]. This would imply that contemporary gantry concepts with rotational speeds of about 1 rotation-per-minute are not applicable for pluri-directional UHDR delivery. Swift pluri-directional UHDR beam delivery within a short overall delivery time has been proposed using multiple fixed beam lines, multiple accelerators [24–26] or with novel stationary or rotating gantry concepts [17,27,28]. However, such swift pluri-directional concepts entail additional technological challenges and may render UHDR devices more bulky and costly than equivalent mono-directional solutions.

Feasibility and benefits of combined photon-electron beam RT have been demonstrated in CDR delivery settings [29–32]. With the aim to identify alternative UHDR treatment approaches for deep-seated tumours, we explore in the present study treatment planning feasibility and dosimetric quality of hybrid UHDR-CDR (HUC) treatment schemes using combined electron and photon beams. The rationale being that a bulk dose can be delivered by a UHDR beam in a less conformal manner to achieve the FLASH effect and can then be complemented by a CDR intensity modulated RT technique aimed at achieving an enhanced dosimetric target coverage and conformity.

To evaluate feasibility and dosimetric plan quality, this study explores in a first step HUC treatments that deliver for every treatment fraction a single broad UHDR electron beam (case-dependent energy between 20 and 250 MeV) together with a CDR volumetric modulated arc therapy (VMAT). Dosimetric plan quality of the resulting HUC dose distributions was assessed across different body sites by comparing to standard of care RT (i.e., clinically delivered plans using the same fractionation scheme). In the second part, quantitative considerations are made regarding a possible FLASH sparing effect for a "HUC boost" treatment that consists of a single fraction UHDR electron boost that is complemented on other days by multiple fractions of CDR VMAT.

## Materials and methods

### *Simulated treatment machines*

Treatment planning was performed using research version of RayStation (RayStation 12A DTK, RaySearch Laboratories, Sweden) [33]. Treatment planning for CDR VMAT plans and for UHDR electron plans with energies up to 20 MeV was conducted with a machine model of a Varian TrueBeam using a multi-leaf collimator (MLC). While there are to date no clinical UHDR VHEE beams available, several projects have set out to design and build UHDR VHEE devices for clinical purposes in the forthcoming years [18,24,25,34–38]. In the absence of existing UHDR VHEE machines that provide dose distributions suitable for clinical use, we created a machine model that simulates 3D-conformal broad electron beams of 20–250 MeV with a homogeneous parallel fluence. Beams were collimated with a fully absorbing MLC placed at 60 cm from the isocentre. Electron dose computations were performed using the clinical RayStation electron Monte Carlo dose engine (v4.0) for electrons up to 20 MeV [33] and its research version that was extended to electron energies up to 250 MeV (v5.4) [26,39,40]. Both engines compute dose-to-water [33].

### *Patient cases and CDR reference plans*

A glioblastoma, a pancreatic cancer, and a localized prostate cancer from our institutional data base were used to evaluate feasibility and dosimetric performance of HUC treatments. Selection criteria included simple, mostly round planning target volumes (PTV) that may be covered by a single electron beam and the possibility to envisage a hypofractionated treatment approach that may increase sparing by FLASH [2,41–43]. To evaluate the dosimetric performance of HUC treatments compared to standard of care RT, we used clinically delivered plans and fractionation schemes as CDR reference plans for these patient cases. Case and reference plan details are summarized in Table 1.

### *Treatment planning and dosimetric evaluation of HUC treatments*

HUC treatment plans were created following the clinically-used prescription, fractionation scheme, and using institutional clinical goals largely based on RTOG and QUANTEC [44]. HUC treatments consisted for every treatment fraction of a single broad electron beam complemented by a VMAT to deliver a normofractionated dose to the PTV. Plan optimization and evaluation was conducted as follows. First, a single UHDR electron beam was manually selected (energy, beam incidence and size) to facilitate target coverage while sparing organs-at-risk (OAR) and limiting tangential incidence on the patient's skin, following thereby typical planning criteria for conventional 3D-conformal RT (3D-CRT). The resulting electron beam dose distribution was then complemented by a CDR VMAT plan that was optimized based on the optimization objectives for the respective clinical reference plan while using the electron dose as background dose, see Table 1. The relative contributions were manually optimized with the goal to deliver the majority of the dose with the UHDR electron beam while ensuring flexibility for the CDR VMAT to achieve acceptable PTV coverage ($V_{95\%}$ within 1 % of the CDR reference plan), conformity and OAR sparing. This meant increasing the weight of the UHDR electron beam if it did not substantially compromise the overall dose distribution compared to the CDR reference plans.

Dosimetric plan quality was assessed based on absorbed dose distributions, dose-volume histograms (DVH), and respective dose metrics comparisons with reference plans. For the PTV, we evaluated $V_{95\%}$, the homogeneity index $HI_{98\%} = D_{98\%}/D_{2\%}$, and the conformity indices $CI_{95\%}$ and $CI_{50\%}$, calculated as $CI_X = V_{PTV,X}/V_{X,}$ where $V_{PTV,X}$ is the PTV volume covered by isodose X and $V_X$ is the total isodose X volume. For OAR, we evaluated $D_{2\%}$, $D_{mean}$ and other organ-specific institutional clinical planning goals (Supplementary Table 1). For HUC plans, we also evaluated dose distributions and dose metrics for the parts of the doses that were delivered by the UHDR electron beam and by the CDR VMAT.

### *Assessment of FLASH sparing by "HUC boost" treatments*

With the aim to provide estimations of possible FLASH sparing effect sizes achievable with HUC treatments, we used the glioblastoma patient case as an example. To this end, we assumed a FLASH normal tissue

**Table 1**
Summary of some of the key patient case and plan characteristics.

| Case | PTV size ($cm^3$) | Prescribed dose (Gy) and normalization | Fractions | Reference plan | HUC plan |
|---|---|---|---|---|---|
| Glioblastoma | 177 | 60 ($D_{median,\ PTV}$) | 30 | Tomotherapy (RadiXact) | 20 MeV $e^-$ + VMAT 6 MV |
| Pancreas cancer | 9.8 (50 Gy) 159 (45 Gy) | 50 ($D_{median,\ PTV}$) | 25 | VMAT 6 MV (Elekta Synergy) | 50 MeV $e^-$ + VMAT 6 MV |
| Prostate cancer | 90.6 | 78 ($D_{median,\ PTV}$) | 39 | VMAT 10 MV (Elekta Synergy) | 250 MeV $e^-$ + VMAT 10 MV |

Abbreviations: HUC = hybrid ultra-high dose rate-conventional dose rate, PTV = Planning target volume, VMAT = volumetric modulated arc therapy.

sparing effect that follows the sudden effect transition (SET) parametrization as a function of fraction dose $D$ [2] and that the SET parametrization can be used for a given UHDR treatment fraction to compute associated isoeffect dose ratios, hereafter termed FLASH-modifying factors (FMF), on a voxel-by-voxel basis in the patient anatomy. This follows an approach analogous to the relative biological effectiveness used for proton and ion beam therapy [45]. The SET parametrization is given by

$$\mathrm{FMF}(D)_{\mathrm{FMF}^{\min},D_T} = \begin{cases} 1 \text{ for } D \le D_T \\ \left(1-\mathrm{FMF}^{\min}\right)\dfrac{D_T}{D} + \mathrm{FMF}^{\min} \text{ for } D > D_T \end{cases}$$

where $D_T > 0$ is the threshold dose for FLASH normal tissue sparing and $\mathrm{FMF}^{\min} \le 1$ is the asymptotic minimum FMF (i.e., maximum FLASH sparing) for high doses [2]. The FMF-weighted dose, that is FMF × dose, represents then the isoeffective CDR dose distribution for normal tissue effects. FMF were computed for two scenarios. For Scenario A, we used a fit of the SET parametrization to pooled mammalian data [2], i.e., $D_T$ = 11.3 Gy and $\mathrm{FMF}_{\min}$ = 0.60. Broad UHDR electron beams can be delivered with dose rates well above 100 Gy/s [10,11,18] and several studies indicate a saturation of FLASH sparing at such high dose rates [46]. Since the fit of the SET parametrization is based on pooled mammalian data with a time-averaged dose rate above 40 Gy/s as inclusion criterion [2], we did not model any dose rate dependency. Brain sparing by FLASH down to fraction doses as low as 3 Gy per fraction has been recently reported [47,48]. An onset of sparing at 3 Gy per fraction with the same maximal sparing for high doses was considered therefore as a more favourable Scenario B for FLASH sparing, i.e., $D_T$ = 3 Gy and $\mathrm{FMF}_{\min}$ = 0.60. The UHDR part of the HUC boost treatment was created using a single fraction UHDR electron boost of 15 Gy ($D_{2\%}$ of PTV) that is complemented by 26 fractions of a CDR VMAT treatment to reach $V_{57\ \mathrm{Gy\ (EQD2)}}$ >95 % (with α/β = 8 Gy) for the PTV. CDR VMAT optimization was performed using the electron boost dose as background dose. For a quantitative comparison of the HUC treatment with the CDR reference plan (see Section 2.B), equivalent dose in 2-Gy-fractions (EQD2) dose summation [33] of the UHDR and CDR dose distributions were performed using α/β = 2 Gy for normal tissues[1] [49] and α/β = 8 Gy for glioblastoma [50], while assuming a FLASH normal tissue sparing effect according to Scenario A and B for the 15-Gy-electron boost.

## Results

For the glioblastoma and the pancreatic cancer case, selecting an electron beam energy that matched the distal dose fall-off of the electron beam to the PTV (i.e., 20 and 50 MeV) provided a conformal electron dose distribution. Instead for the prostate case, rectum, anal canal, and bladder sparing was achieved by a 250 MeV electron beam taking advantage of its sharper lateral penumbrae. Absorbed dose distributions and DVH obtained for the HUC and the CDR reference treatments are shown for the glioblastoma, the pancreatic cancer, and the prostate cancer case in Figs. 1, 2, and 3, respectively. For the HUC treatment plans, this includes dose distributions for both the whole treatment and UHDR doses delivered by the electron beam alone. Corresponding dose metrics are provided in Supplementary Table 1. All HUC plans achieved similar PTV coverage ($V_{95\%}$ within 0.5 %) and homogeneity ($HI_{98\%}$ within 0.02 for high dose PTV) compared to the reference plans and OAR doses were always below the applied clinical goals. Mean doses to the body were lower for the glioblastoma (−8 %) and the pancreatic cancer (−3 %) HUC plans, and higher for the HUC prostate plan (18 %) when compared to CDR reference plans. DVH metrics of critical OAR that received substantial doses were mostly similar to the CDR reference plans. An exception to this were the femoral heads, for which doses were substantially increased due to the lateral HUC electron beam ($D_{2\%}$ to femurs of 55.5 Gy (right) and 58.5 Gy (left)). For all three tested cases, the HUC plans could deliver the majority of the dose to the PTV ($D_{\mathrm{median}}$ of 50–69 %) and large parts of doses to adjacent tissues at UHDR, particularly in the high dose region receiving more than 80 % of the prescribed dose (e.g., brain $D_{2\%}$ of 49.3 Gy for UHDR dose versus 30 Gy for CDR dose).

For the glioblastoma treatment with a 15 Gy UHDR electron boost, the magnitude of normal tissue sparing achieved by FLASH differs markedly between Scenario A and B, see Fig. 4**(a–d)**. For Scenario A, sufficiently high doses for normal tissue sparing by FLASH are only reached by the 15-Gy-electron boost in the central region of the PTV and the achieved sparing magnitude was moderate (10 % for $D_{2\%,\mathrm{PTV}}$, 6 % for $D_{2\%,\mathrm{Brain}}$). Instead for Scenario B, FMF-weighted doses to healthy brain tissues inside and outside the PTV are substantially reduced (32 % for $D_{2\%,\mathrm{PTV}}$, 31 % for $D_{2\%,\mathrm{Brain}}$, and 25 % for $D_{2\%,\mathrm{Brain\text{-}PTV}}$).

Resulting EQD2-volume-histograms (EQD2-VH) for the HUC boost treatment and the CDR reference plan are displayed in Fig. 4**(e–g)**. This representation accounts for fractionation effects of the whole treatment schedule. In this representation (with α/β = 8 Gy), PTV coverage is the same for both schedules (i.e., $V_{57\ \mathrm{Gy\ (EQD2)}}$ is 98 %) and median EQD2 to the PTV is escalated by 11 % for the HUC boost. For Scenario B, similar EQD2-VH are achieved for central nervous system tissues (with α/β = 2 Gy), representing the principal OAR for this case. While the normal tissues outside the PTV (i.e., Brain-PTV volume) receive also similar EQD2 to the ones of the CDR reference plan for Scenario A, there is a substantially increased maximum EQD2 for normal tissues inside the PTV (39 % for $D_{2\%,\mathrm{Brain}}$) compared to the clinical reference plan.

## Discussion

Next to eliciting a pronounced FLASH effect, UHDR treatments need to take care that dosimetric plan quality is not substantially degraded compared to standard of care RT since this may counteract a potential therapeutic gain by the FLASH effect. Indeed, the desirable case would be that the FLASH effect is added to a standard of care conformal dose distribution. This study demonstrates that hybrid treatments combining an UHDR electron field with a CDR VMAT may provide dosimetrically conformal treatments for tumours with simple shapes in various body sites and depths in the patient while delivering the majority of the prescribed dose per fraction (PTV $D_{\mathrm{median}} \ge 50$ %) at UHDR without delivery pauses. Moreover, geometric sparing of critical OAR in the high dose region was comparable to that of standard of care RT treatments. A potential normal tissue sparing by FLASH can therefore be expected to be on top of the similar geometric sparing and would not need to compensate a lack thereof.

The combined delivery of CDR electron and photon beams using MLC collimation was shown to be able to improve dosimetric plan quality compared to photon-only plans and has been implemented clinically [29–32]. Existing converted clinical UHDR and dedicated UHDR linear accelerators that fit in conventional clinical vaults are capable of delivering broad UHDR electron beams at the isocentre with energies of ~4–20 MeV to extended target sizes of 10 cm and beyond [10–14]. Such proven and established technology could be used to deliver UHDR electron beams required for HUC treatments and could be further extended in terms of achievable UHDR field sizes and beam energies. In this respect, dual-use clinical linear accelerator-based concepts that can deliver both CDR VMAT treatments and UHDR electron beams [10] during a treatment session to an immobilized patient appear particularly appealing. Such concepts can reduce dosimetric uncertainties and streamline the clinical workflow compared to solutions using two separated machines that require a second patient immobilization within a fraction. Currently, UHDR VHEE beams are not yet a clinical reality, but several projects have set out to design and build the first clinical

[1] The choice of α/β = 2 Gy has been made as a worst-case scenario for glioblastoma cases because of the possible proximity of neurological structures, such as optic nerves, chiasm, brain, and brainstem.

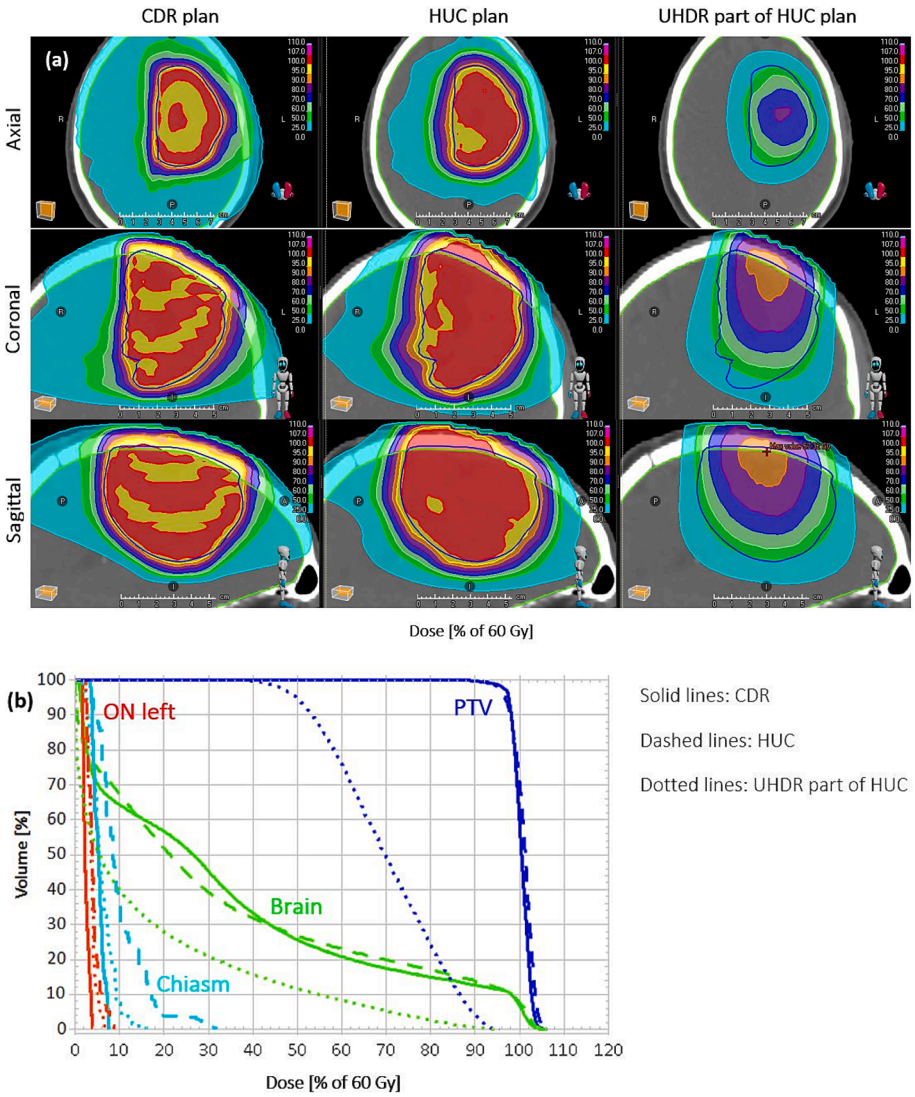


**Fig. 1.** Dosimetric comparison of a conventional dose rate (CDR) helical tomotherapy plan and a hybrid ultra-high dose rate (UHDR)-CDR (HUC) plan for a glioblastoma patient. Axial, sagittal, and coronal dose distributions **(a)** and dose-volume histograms (DVH) **(b)** are shown for the CDR plan, for the HUC plan, and for UHDR part of the HUC plan that is delivered by a 20 MeV TrueBeam electron field. Abbreviations: ON = Optical nerve, PTV = Planning target volume.

UHDR VHEE devices [18,24,25,34–38]. These devices will be capable of delivering mono-directional VHEE fields on sub-second time scales, as needed for HUC treatments investigated in this work. VHEE treatments alone are in principle able to deliver dosimetrically conformal treatments [16,26,51,52]. However, swift pluri-directional VHEE beam delivery on sub-second time scales, as might be required for an optimized FLASH sparing [21–23], may be technically challenging, bulky, and costly, as previously mentioned. Other UHDR beams could also be used for HUC treatment approaches, in particular UHDR protons combined with CDR protons or VMAT [17,19]. Except for few studies [47,48], normal tissues sparing by FLASH is so far a phenomenon principally reported in preclinical models for large fraction doses ($\gtrsim$ 5 Gy) and some data that suggest that the magnitude of sparing by FLASH may increase with single fraction dose [2,23,53,54]. Standard of care normofractionated RT fractionation schemes, as used for dosimetric comparison in Figs. 1, 2, and 3, may therefore be suboptimal to achieve a pronounced FLASH sparing effect. While those HUC plans that apply an UHDR electron beam and a VMAT for each fraction were generated based on normofractionated treatment schemes, their relative dose distributions, which define their dosimetric performance and quality, will not change when rescaled to more hypofractionated delivery schemes and the corresponding findings remain equally applicable. For the case that large doses per fraction are needed to optimize FLASH sparing, HUC treatment schemes that deliver a large single fraction electron boost at UHDR to achieve a pronounced FLASH effect complemented by normofractionated CDR VMAT treatments may be preferable. The presented HUC boost glioblastoma treatment (Fig. 4) illustrates that such a strategy may result for the UHDR electron boost in a pronounced normal tissue sparing by FLASH for Scenario B, but only in a smaller sparing for Scenario A (Fig. 4**(a–d)**). A potential disadvantage of hypofractionated treatment schedules is that they are known to increase the radiobiological damage to late-reacting tissues compared to normofractionated treatments for many clinical scenarios [56,57]. Accordingly, the EQD2 representations of the HUC boost treatment indicate that the sparing of normal tissues by FLASH may be counteracted by fractionation effects (Fig. 4**(e-g)**). Effect sizes of normal tissue sparing by FLASH and by fractionated treatments have been compared more systematically elsewhere [55]. Based on the linear-quadratic model, those comparisons indicate that for many clinical scenarios a considerable normal tissue sparing by FLASH (~15–30 %) is required to counteract the increased radiobiological damage experienced by late-reacting normal tissues for hypofractionated UHDR treatments when comparing to normofractionated CDR treatments that are equieffective to the tumour.

An inconvenience of HUC treatments is that not all dose is delivered

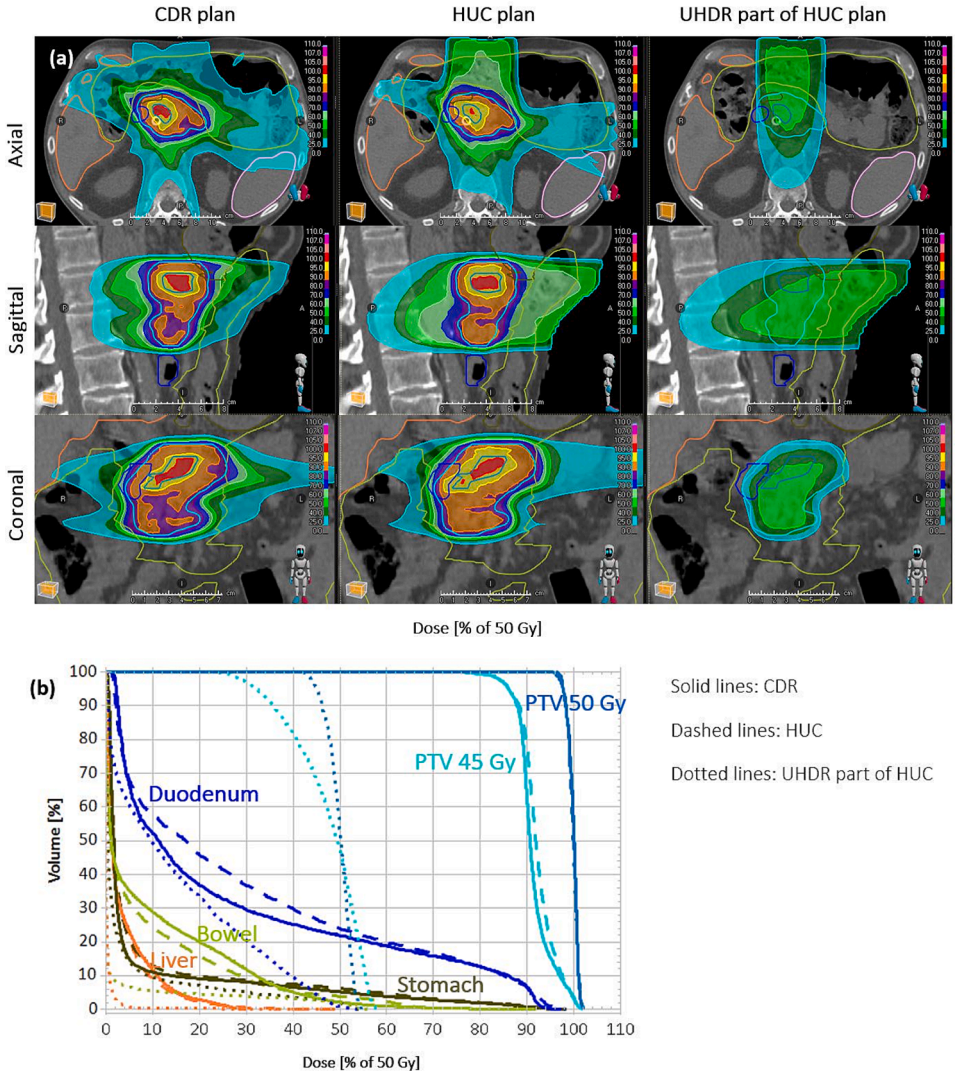


**Fig. 2.** Dosimetric comparison of a conventional dose rate (CDR) volumetric modulated arc therapy (VMAT) plan and a hybrid ultra-high dose rate (UHDR)-CDR (HUC) plan for a pancreatic cancer. Axial, sagittal, and coronal dose distributions **(a)** and dose-volume histograms (DVH) **(b)** are shown for the CDR plan, for the HUC plan, and for UHDR part of the HUC plan that is delivered by a 50 MeV electron field. Abbreviations: PTV = Planning target volume.

at UHDR. This will decrease the achievable magnitude of the FLASH effect compared to a dosimetrically equivalent treatment that delivers the whole dose at UHDR without delivery pauses. Furthermore, the UHDR electron beam of a HUC treatment tends to deliver the highest doses in the central part of the PTV while delivering less dose to normal tissues in the high dose region in the vicinity of the PTV border that could benefit from a FLASH sparing.

There are several limitations to the present study. No optimization technique was used to assure optimality of both clinical and HUC plans and the proposed HUC treatment approach was only evaluated for three selected patient cases using partially idealized electron beam models. While this enabled us to demonstrate the dosimetric feasibility of HUC treatments, larger-sample treatment planning studies will be needed to assess its performance in more detail. The presented HUC treatment approach is only applicable to selected tumour sites and relatively simple tumour shapes. However, intensity- and range-modulated electron beams together with more sophisticated combined beam optimization approaches [16,29,30,58,59] will likely improve the UHDR dose contribution, coverage and conformity, as well as overall plan quality substantially compared to the ones presented in this study. For instance, a range-modulated electron beam would have allowed us to match the distal dose fall-off of the electron beam better to the distal part of the PTV for the glioblastoma and the pancreas case (see 'UHDR part of the HUC plan' in the Fig. 1**(a)** and Fig. 2**(a)**). Similarly, intensity-modulation of the electron beam would have allowed us to improve also transversal target coverage and homogeneity of the electron beams. Enhanced tailoring of the UHDR electron beam to the PTV will also increase applicability of HUC treatments further to encompass more challenging tumour shapes and sites. Feasibility of intensity- and range-modulation for UHDR electron beams has been recently demonstrated for canine treatments [59]. Another approach to HUC planning is to concentrate the delivery of the UHDR electron beam component that may elicit the FLASH effect only to a specific part of the PTV that has a critical OAR (e.g., with dose limiting toxicity) in vicinity. Such an approach may again increase dosimetric performance of HUC treatments and enlarge its applicability. Previous works have shown that jointly optimized CDR photon and electron beams may dosimetrically outperform CDR IMRT and VMAT treatments [29,30]. This may be also achievable for jointly optimized HUC treatments thereby providing potentially an additional clinical rationale for HUC treatments for specific patient cohorts. While we applied clinically used margins for this study for HUC plans, HUC plan robustness will differ compared to conventional treatments and margin and robustness strategies specific to HUC treatments may be more appropriate. It has been shown that robust

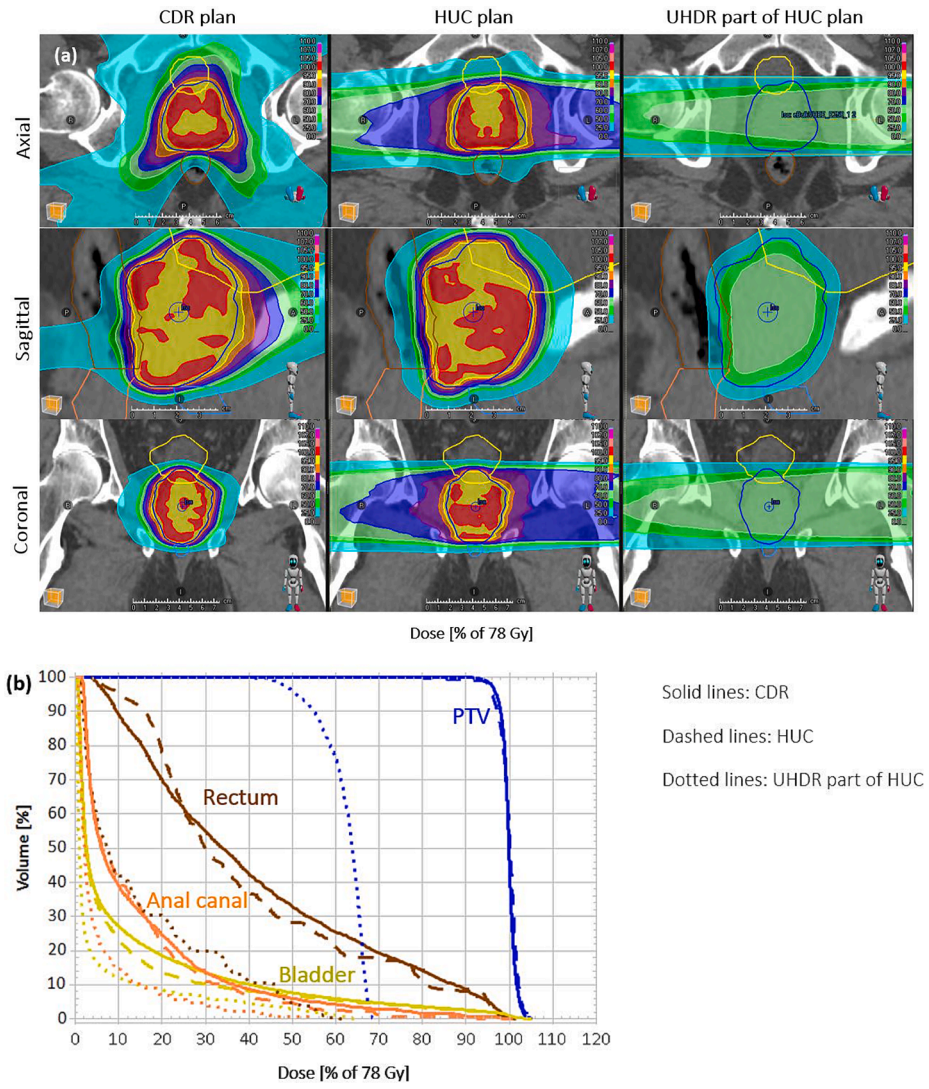


**Fig. 3.** Dosimetric comparison of a conventional dose rate (CDR) volumentric modulated arc therapy (VMAT) plan and a hybrid ultra-high dose rate (UHDR)-CDR (HUC) plan for a prostate cancer patient. Axial, sagittal, and coronal dose distributions **(a)** and dose-volume histograms (DVH) **(b)** are shown for the CDR plan, for the HUC plan, and for UHDR part of the HUC plan that is delivered by a 250 MeV electron field. Abbreviations: PTV = Planning target volume.

plans can be achieved for jointly optimized CDR photon and electron beams [30].

This study shows that simple, mostly convex and round target shapes are well-suited for HUC treatments, as they can be effectively covered by a broad UHDR electron beam without requiring range or intensity modulation or using a partial-target irradiation approach (see above). As illustrated by the glioblastoma and the pancreas case, lower-energy electron beams may be used to align the distal dose fall-off of the electron beam with the distal PTV boundary for shallow to medium tumour depths. However, oblique beam incidences and anatomical heterogeneities may exacerbate coverage for such an approach. In other cases, such as prostate cancer, VHEE beams with their sharper lateral dose gradients may be better suited to efficiently spare critical organs near the PTV. More advanced HUC delivery and optimization methods (discussed earlier) can improve overall dosimetry and UHDR dose distribution compared to this study, enabling thereby also the treatment of more complex target shapes. Further treatment planning studies are needed to identify the most suitable patient cohorts and approaches for HUC treatments. In this context, optimization of the fraction delivery scheme and expected FLASH effect sizes for a given cohort will need additional consideration. To date, there is little knowledge about FLASH effect sizes achievable for clinical settings and fractionated treatments [1,2,47,54]. Therefore, FLASH sparing of normal tissues was assessed in this study by applying FMF values obtained from a fit to preclinical observations (mostly rodent models) on a voxel-by-voxel level to clinical patient cases and utilizing subsequent representations as EQD2. This entails multiple implicit assumptions and simplifications that may not be applicable to clinical patient cases and toxicities [2,3,55]. The two, substantially differing scenarios used for FLASH sparing in this work may therefore be emblematic for the large uncertainties associated currently with quantifications of the FLASH effect in clinical settings.

## Conclusion

UHDR electron beams and CDR photon VMAT can be combined to deliver hybrid UHDR-CDR dose distributions for selected patient cohorts with a dosimetric plan quality comparable to the one of standard-of-care treatment plans while delivering the bulk dose ($D_{median,PTV} > 50$ %) at UHDR using a single broad electron beam. This UHDR part of the treatment may then result in an additional sparing of normal tissues by FLASH in the high dose region inside and in vicinity of the PTV. HUC treatments may therefore be a viable approach for lowering the technical burdens to achieve dosimetrically conformal UHDR delivery for the initial clinical exploration of FLASH therapy.

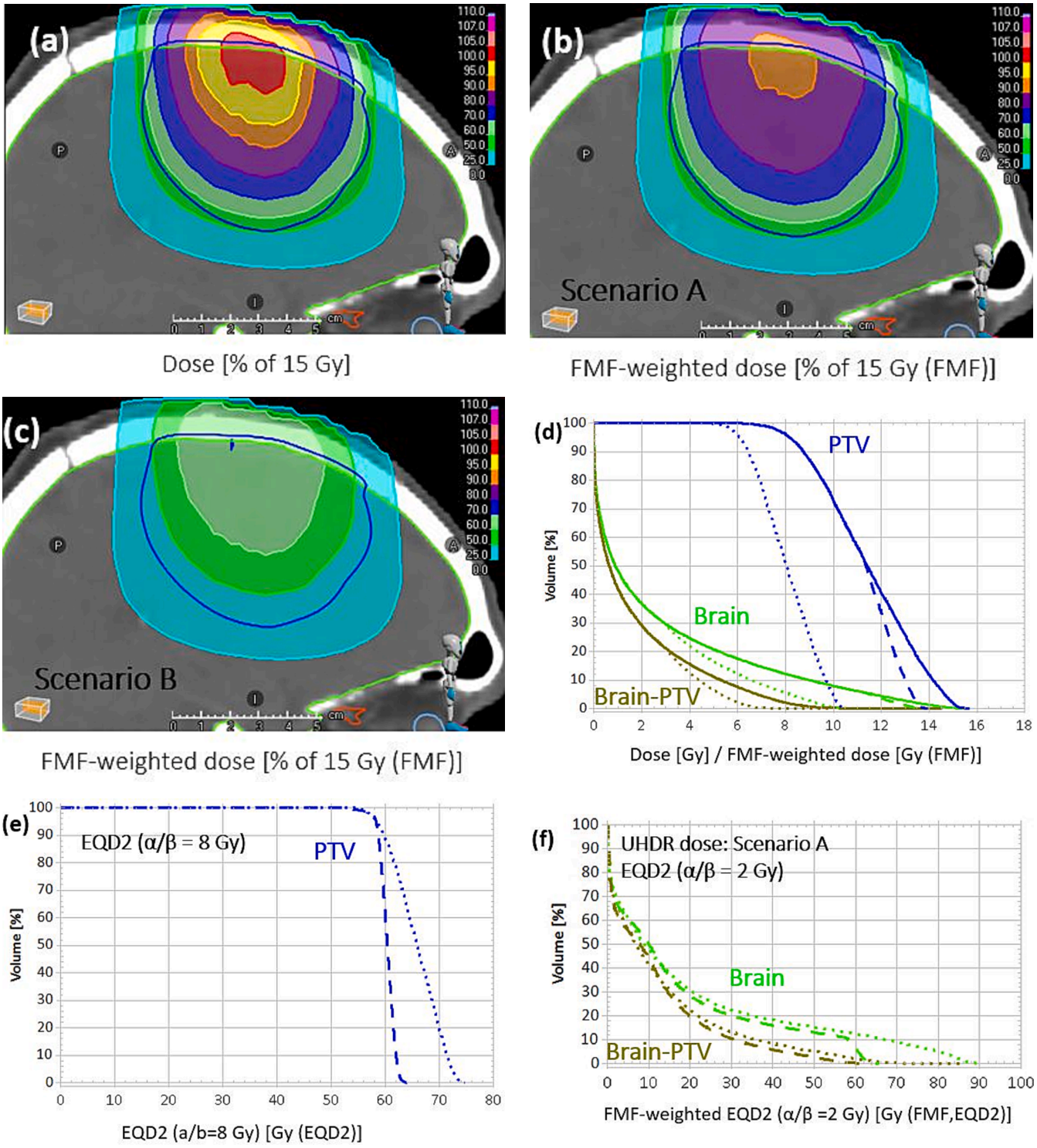


**Fig. 4.** Sagittal absorbed dose distribution **(a)** and FMF-weighted dose distribution for Scenario A **(b)** and Scenario B **(c)** for a 15 Gy ultra-high dose rate (UHDR) electron boost for a glioblastoma case (percentage of 15 Gy and 15 Gy (FMF)). For illustration purposes, FMF-weighted dose distribution are presented applying a FLASH sparing also inside the PTV that is to a large part composed of healthy brain tissues. The respective dose-volume histograms (DVH) for the PTV, the brain, and the brain minus the PTV (brain-PTV) are shown in panel **(d)** for the electron boost for the absorbed dose (solid lines) and for FMF-weighted dose Scenario A (dashed lines) and Scenario B (dotted lines). EQD2-weighted DVH ($\alpha/\beta = 8$ Gy) for the hybrid UHDR-CDR (HUC) boost plan (dotted lines) and the conventional dose rate (CDR) clinical plan (dashed lines) are presented in panel **(e)** for the PTV. EQD2-weighted DVH ($\alpha/\beta = 2$ Gy) for the brain and brain-PTV for the clinical reference plan (dashed lines) and for the HUC boost plan (dotted lines) applying a FLASH sparing for the UHDR electron boost according to Scenario A **(f)** and Scenario B **(g)**. Details see text. Abbreviations: EQD2 = Equivalent dose in 2 Gy fractions, PTV = Planning target volume.

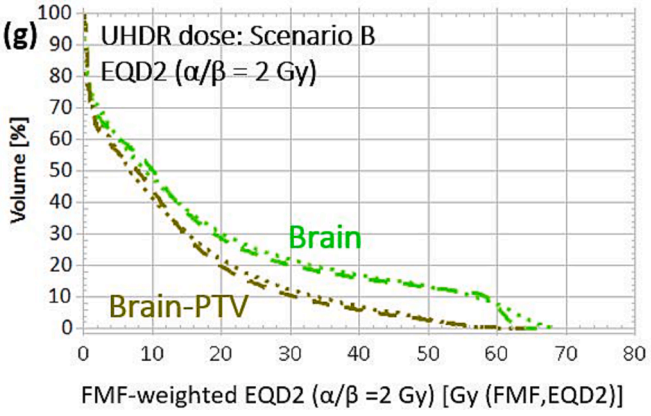


**Fig. 4.** (*continued*).

## Authors contributions

All authors have made substantial contributions to the conception and design of the study. They all have been involved in drafting the manuscript or revising it critically for important intellectual content and have given final approval of the version to be published.

## CRediT authorship contribution statement

**Till Tobias Böhlen:** Writing – review & editing, Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Michele Zeverino:** Writing – review & editing, Software, Resources, Methodology, Investigation, Formal analysis. **Jean-François Germond:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **Rémy Kinj:** Writing – review & editing, Validation, Methodology, Conceptualization. **Luis Schiappacasse:** Writing – review & editing, Validation, Methodology, Conceptualization. **François Bochud:** Writing – review & editing, Validation, Methodology, Conceptualization. **Fernanda Herrera:** Writing – review & editing, Methodology, Conceptualization. **Jean Bourhis:** Writing – review & editing, Validation, Methodology, Formal analysis, Conceptualization. **Raphaël Moeckli:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110576.

## Data availability

Data will be made available on reasonable request.

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