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Review Article

FLASH radiotherapy treatment planning and models for electron beams

Mahbubur Rahman [a,1], Antonio Trigilio [b,c,1], Gaia Franciosini [b,c], Raphaël Moeckli [d,*], Rongxiao Zhang [a,e], Till Tobias Böhlen [d]

[a] Thayer School of Engineering, Dartmouth College, Hanover, NH, USA; [b] Physics Department, "La Sapienza" University of Rome; [c] INFN National Institute of Nuclear Physics, Rome Section, Rome, Italy; [d] Institute of Radiation Physics, Lausanne University Hospital and Lausanne University, Lausanne, Switzerland; [e] Dartmouth Hitchcock Medical Center, Lebanon, NH, USA

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ABSTRACT

The FLASH effect designates normal tissue sparing at ultra-high dose rate (UHDR, >40 Gy/s) compared to conventional dose rate (~0.1 Gy/s) irradiation while maintaining tumour control and has the potential to improve the therapeutic ratio of radiotherapy (RT). UHDR high-energy electron (HEE, 4–20 MeV) beams are currently a mainstay for investigating the clinical potential of FLASH RT for superficial tumours. In the future very-high energy electron (VHEE, 50–250 MeV) UHDR beams may be used to treat deep-seated tumours. UHDR HEE treatment planning focused at its initial stage on accurate dosimetric modelling of converted and dedicated UHDR electron RT devices for the clinical transfer of FLASH RT. VHEE treatment planning demonstrated promising dosimetric performance compared to clinical photon RT techniques *in silico* and was used to evaluate and optimise the design of novel VHEE RT devices. Multiple metrics and models have been proposed for a quantitative description of the FLASH effect in treatment planning, but an improved experimental characterization and understanding of the FLASH effect is needed to allow for an accurate and validated modelling of the effect in treatment planning. The importance of treatment planning for electron FLASH RT will augment as the field moves forward to treat more complex clinical indications and target sites. In this review, TPS developments in HEE and VHEE are presented considering beam models, characteristics, and future FLASH applications.

FLASH radiotherapy (FLASH RT) based on ultra-high dose rate (UHDR) irradiations is actively being studied by the radiotherapy community as one of the most promising break-through technologies for RT cancer treatment [1]. It can potentially improve the sparing of healthy tissues when compared to conventional dose rate (CONV) RT while keeping the same tumoricidal effect [2–5], an observation referred to as the 'FLASH effect'. Preclinical evidence for this differential effect spans multiple beam modalities, biological systems and endpoints [2–5] and led to the treatment of the first patient with electron FLASH RT in 2019 [6]. While photon and proton beams also demonstrated the FLASH effect [7–10], to date, most preclinical evidence comes from studies using 4–20 MeV electron beams, since such UHDR beams can be readily produced by ad-hoc dedicated compact accelerators [11,12] and UHDR-converted medical electron linacs [13,14]. Consequently, such high-energy electron (HEE) beams are currently a mainstay for preclinical research and the clinical transfer of FLASH RT in veterinary and human clinical trials [6,15–18]. There are also efforts towards employing UHDR HEE beams by modified or newly-developed compact systems in an intraoperative RT (IORT) setting [5,11,19–21]. Furthermore, to overcome the limited penetration depth of HEE beams of a few centimetres, very-high energy electron (VHEE) beams of about 50–250 MeV have been proposed to deliver doses to deep-seated tumours with a sharper lateral penumbrae [22–24], see Fig. 1.

While accurate three-dimensional (3D) treatment planning is crucial for the success of modern RT, preclinical UHDR studies as well as initial veterinary and human UHDR treatments have proceeded so far with little to no use of treatment planning and employed only much simpler standardised single field treatments [6,15–17,25]. However, despite the feasibility focus and use of simple treatment sites and schemes for these pioneering studies, the added value of 3D dose distributions is recognized [16]. With the extension of electron FLASH RT treatments to anatomically more challenging treatment sites and to compete with dosimetric conformity achieved by CONV high precision RT, it can be assumed that the development of performant and predictive treatment planning will be a crucial component to catalyse clinical transfer and optimisation of FLASH RT. Furthermore, when shifting from single broad UHDR beam treatments to more complex high-

* Corresponding author at: Institute of Radiation Physics, Lausanne University Hospital, Rue du Grand-Pré 1, CH-1007 Lausanne, Switzerland.
E-mail address: raphael.moeckli@chuv.ch (R. Moeckli).
[1] Shared first authors.

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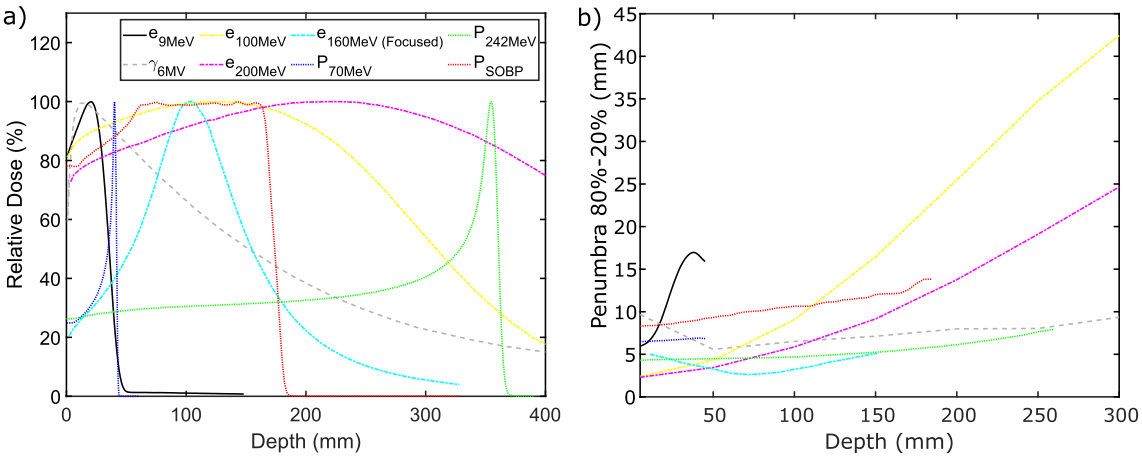

Fig. 1. a) Percentage depth dose (PDD) curves of photon and electron beams and integral depth dose curves of proton beams and a proton spread out Bragg peak (SOBP, with 60–160 cm range). b) Penumbra (distance of 80% to 20% of the maximum) for the lateral profile as a function of depth for respective sources. All curves are for parallel 10 × 10 cm^2 fields, unless specified to be focused [24,97,130].

precision UHDR RT that uses multiple scanned or intensity-modulated beams, UHDR treatment planning will be required to evaluate and optimize temporal aspects of dose delivery and should ideally allow a quantitative assessment of the achieved FLASH effect for a given treatment plan.

In this initial phase, the point of departure, focus, and challenges for physics-aspects of UHDR electron beam treatment planning and beam modelling are largely specific to the electron beam energy and delivery modality. Treatment planning for external UHDR HEE beams can build largely on treatment planning and beam models developed for CONV clinical HEE beams and published studies focussed so far primarily on the accurate modelling of dose distributions from converted and dedicated UHDR RT devices and treatment techniques. Instead, clinical VHEE RT devices do not exist yet and therefore, the purpose of UHDR and CONV VHEE treatment planning studies was so far primarily to evaluate its feasibility and performance *in silico* and to guide and optimise the design of future VHEE RT devices. Furthermore, UHDR treatment planning may account for the FLASH effect quantitatively to be able to optimise the temporal dose delivery structure of FLASH RT devices as well as their case-specific treatment plans and to introduce metrics, which are predictive of clinical outcome.

In the first two sections of this review, we outline physics aspects and challenges of UHDR treatment planning for HEE and VHEE RT and summarise applicable treatment planning approaches with their corresponding delivery techniques, treatment planning systems (TPS), and beam models. In the third section, we focus on biological aspects of UHDR treatment planning by reviewing current approaches to account for the FLASH effect in treatment planning studies and by discussing possible future directions and challenges.

High-energy electron radiotherapy

High-energy electron (4–20 MeV) RT fills in the gap of megavoltage (MV) photon RT and treats shallow tumour volumes. While MV photons exhibit a steep build-up at shallow depths of <2 cm, making treatment delivery at these depths complicated, electron beams with finite range are advantageous for treating shallow tumours. Thus, HEE RT is often utilised for the treatment of superficial lesions below 6 cm depth (see Fig. 1**,** and Fig. 2). Treatment sites include head and neck (e.g. retina, nasal, lip), breast, node boosts, and skin but also other sites such as pancreas and abdominal structures via intraoperative radiation therapy (IORT), vulva, and cervix.

UHDR HEE delivery techniques and challenges

Currently, there are dedicated UHDR HEE devices [11,12,19–21,26] and converted medical linacs repurposed for UHDR HEE [13,14] (see Fig. 2), albeit often with beam characteristics different from those used to treat patients. For example, some UHDR machines produce Gaussian beams with FWHM that can range from a few to about 15 cm, or even more [27–30]. Others produce smaller but flat beams for preclinical treatments and *in vivo* studies. There are established techniques and tools to ensure conformal CONV HEE RT dose delivery and some of them can be equally applied to single fields of UHDR HEE RT to improve conformity [31], see Fig. 3 **a)-d)**. Collimating inserts on applicators or skin collimators allow to reduce side scatter of the beam at depth and reduce thereby dose to surrounding tissue. Multi-leaf collimators (MLC), commonly used for photon beams, can be applied to HEE RT as well to ensure conformality, especially for reduced source-to-surface distances (SSD) [32] or by extending the location of collimation [33]. Bolus can be used to increase dose to the surface while reducing dose distally. Internal shields are used for intraoperative RT and can also prevent dose to critical structures such as salivary glands or the lens of the eye.

However, some methods of ensuring conformal dose delivery to patients may require further investigation of whether the FLASH effect will be achieved and its overall value to ensure superior outcome for patients. For example, there are studies demonstrating the feasibility and use of modulated electron RT, which utilised MLC (sometimes placed close to the patient) to achieve conformal dose to the patient [34,35]. As the UHDR HEE delivery machines currently deliver beam pulses every few milliseconds, and the pulses are typically on the order of one or more Gray-per-pulse, this would require a very fast moving MLC to achieve the desired field modulation and such a technology is not currently yet available [36]. Alternatively, there has been development of intensity modulated passive scattering applicator devices to achieve conformal and homogeneous dose, without compromising substantially maximum depths that can be treated [37,38]. Rahman et al. [39] demonstrated the feasibility of plan and dose calculation with the use of this passive delivery method for an electron UHDR beam produced from a modified medical linac.

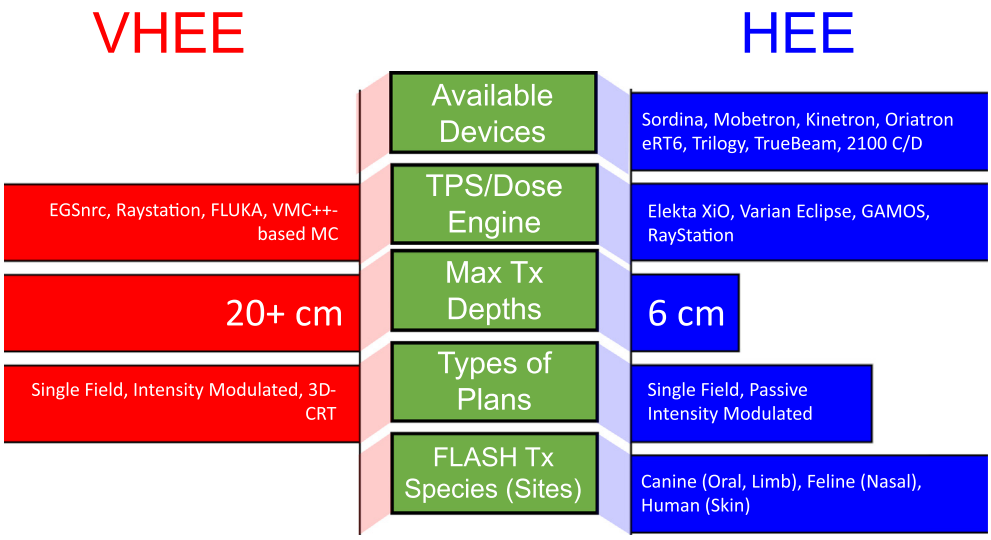

Fig. 2. Comparison of VHEE and HEE; considering devices, treatments, and treatment plans.

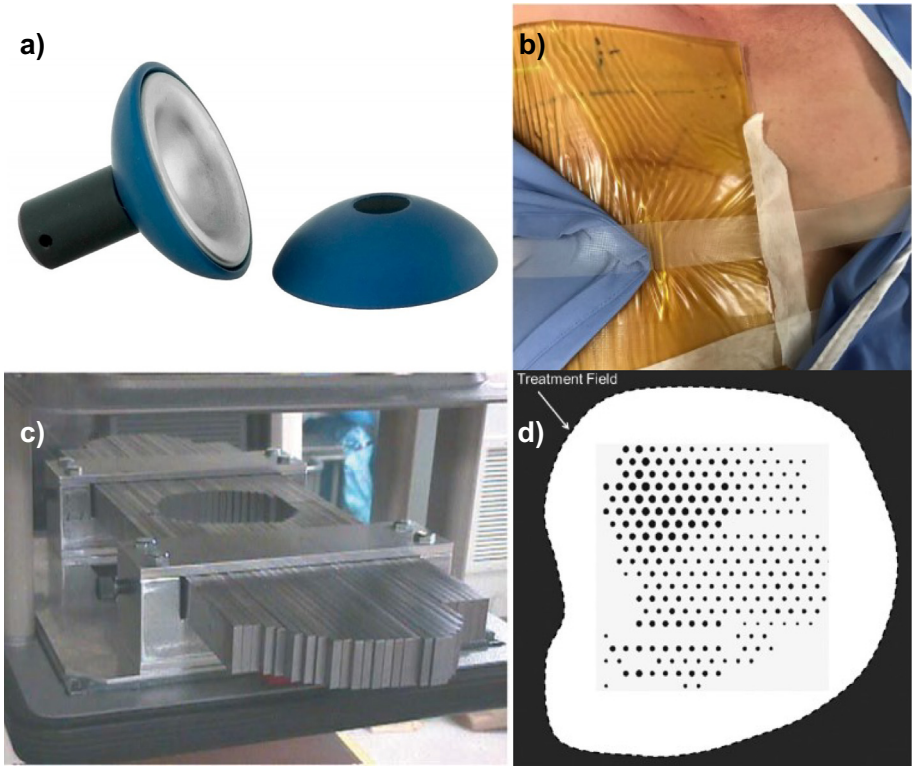

Fig. 3. Tools used for conformality in conventional HEE EBRT including a) eye shield, b) bolus, c) multileaf collimator, and d) passive electron intensity modulating applicator.

Hybrid electron-photon beams are often used for treatments (e.g. partial breast treatment). Currently, UHDR HEE beams are accessible whereas UHDR photon beam technology is lagging. Hence, the benefit of part of the treatment being under FLASH condition may be a question worth exploring. While studies under conventional dose rates showed marginal improvements in normal tissue complication probability (NTCP) [40] with mixed beam treatment and optimization consideration were taken [41], the treatment planning studies may need to be revisited incorporating dose rate's impact in NTCP and optimization with FLASH treatment.

Beside usual external beam irradiation, IORT involves the delivery of the prescribed therapeutic dose concurrently or in the immediate aftermath of the surgical removal of the tumour, with the patient lying on the treatment bed and the operative incision still open, to spare surrounding healthy tissues, enabling direct access to the target zone [42,43]. Amongst all IORT modalities, electron IORT with energies between 4–12 MeV is, as of today, the most used in clinical practice. IORT treatments are routinely delivered as large single fraction doses. They have been proven effective for cases of rectal tumour, retroperitoneal sarcoma, breast cancer, pancreatic lesions and selected cases of abdominal tumours [44–46]. Furthermore, it was shown that conventional clinical

mobile IORT linacs can be converted into UHDR devices [11,47]. This makes electron beam IORT a promising candidate modality in the initial phase of the clinical transfer of FLASH RT. Enabling IORT treatment planning could facilitate a more accurate and optimised delivery, thereby potentially improving spatial dose conformity, prescription and reporting of delivered dose distributions [48]. Documentation of administered IORT dose distributions and temporal delivery aspects would also allow a better retrospective correlation with clinical outcome. However, it is difficult to obtain a TPS to fully exploit IORT potential. The reason lies primarily in the limited time available during surgery (order of minutes) to both obtain the imaging of the surgical field and perform dose optimization through the TPS computation. Nevertheless, there are efforts to tackle the challenges of this task [48,49].

Beam models of HEE RT

Since electron therapy predates fast computing technology, there has been a progression of radiation transport and absorbed dose calculation for electron beam modelling and dose calculation. Brahme's analytical models applying Fermi-Eyges theory of the electron beam transport incorporating multiple coulomb scattering first influenced machine design [50]. Since then there has been a transition from the late 1960′s to use Monte Carlo (MC) simulations to predict absorbed dose. However, tissue heterogeneity was still not well accounted for, assuming either water equivalency or 1D slabs of varying density the electron beam would propagate through. By the mid 1970′s, dose from pencil beams were summed to predict dose to patients and model a broad beam [51]. Since the initial demonstration of voxel based MC calculation to patients by Kawrakrow et al. [52], there has been an adoption of fast MC methods of modelling the beam and dose calculation to patients incorporating tissue heterogeneity from CT scans [53,54]. Computer speed has increased enough to make MC methods become the gold standard for electron linac treatment head simulations, beam modelling in the TPS, and dose calculation of electron beams in patient anatomies [55]. Consequently, approaches based on MC methods are well established for HEE RT for these tasks and most recent research and clinical HEE beam models apply MC codes for particle transport in the treatment head as well as particle transport and dose computations in the patient [16,28,29,55,56].

As previously outlined, dedicated UHDR HEE devices [11,12,19–21,26] and medical linacs repurposed for UHDR HEE [13,14] have treatment heads and beam characteristics that are different from those used to treat patients. This makes it necessary to develop and commission dedicated treatment head and beam models that are unique to the current experimental and converted machines. In the context of UHDR electron FLASH RT, so far, published studies focussed on an accurate modelling of dose distributions produced by these UHDR devices. There are several UHDR electron beam models used to treat clinical (human and animal) patients, both commercial and research, see Table 1 and Fig. 2. Future UHDR HEE machines could benefit of a more standardised and unified approach, so that beam modelling could be less dependent of the machine and the experimental set-up.

Current and future UHDR HEE treatment planning

While superficial skin lesions lend themselves for initial clinical transfer of UHDR HEE RT, in principle, all clinical cases that are treated nowadays with CONV HEE RT are potential candidates for UHDR HEE RT, given a clinical rationale and expected clinical benefit that justifies the use of such a new experimental technique. The first human receiving FLASH RT was a lymphoma patient treated on the limb with a 6 MeV UHDR electron beam [6] and metastases of melanoma are currently being treated within a human clinical trial using a 9 MeV UHDR electron beam [18].

However, other treatments such as partial breast, cavity or scar boost, total limb irradiation, total skin electron therapy (TSET) that are delivered with HEE in conventional dose rates bring about a few questions. For example, can the FLASH effect apply to a part of a treatment regimen like in partial breast and boost irradiation as there is currently no full field photon FLASH? Furthermore, there is no technology that can produce UHDR at distances at which TSET treatment of mycosis fungoides is done with a large field to cover nearly the entire body [33]. There is also no technology that can produce multiple fields via gantry rotation in less than a second for total limb irradiation under UHDR conditions. Thus, HEE electron beams are currently limited to single field beams but can be modulated with devices described in the previous section.

Animal patient trials are clinically meaningful to investigate FLASH RT benefits via transferable treatment planning even for single field deliveries. UHDR treatments of veterinary patients via HEE beams indicate the importance of treatment planning, especially for single field irradiations. Rohrer Bley et al. showed their treatment of feline's resulted in late toxicity probably due to hot spots created by heterogeneities indicating that imaging and treatment planning could be synergistically applied with FLASH delivery to potentially improve patient outcome [16]. Konradsson et al. [17] treated several canine patients, which included sites such as oral (mandible), eyelid, and ears, where dose calculation can inform how to best treat and preserve organs-at-risk.

Table 1 summarises TPS and dose engines that have been implemented for UHDR HEE beams thus far. The first implementation of treatment planning with an experimental UHDR beam was for a mini pig and cats by Vozenin et al. [57]. Rohrer Bley et al. [16] also utilised a TPS for retrospective dose reconstruction (see above). The first beam model of an UHDR beam from a converted medical linac was developed by Rahman et al. on the Varian commercial TPS [28] and compared dose distributions for both CONV and UHDR HEE beam delivery. An example of a canine patient plan using this TPS is shown in Fig. 4. Furthermore, Rahman et al. [39] quantified homogeneity and conformality for treatment plans comparing passive intensity modulated and single field electron FLASH beams, further exploring potential treatment sites for UHDR beams. Nonetheless, the commercial TPS that are being developed by vendors may accelerate and ease the adoption of MC-based treatment planning for UHDR HEE RT devices, see Table 1 **a**). In future, UHDR HEE treatments may shift from using single collimated broad beams to more complex delivery techniques including intensity modulation and multiple beams. Incorporating dose rate and including dose delivery dynamics will become more pertinent for such treatments (see later).

Very-high energy electron radiotherapy

VHEE beams for RT have first been proposed more than two decades ago [22,58–61], since it was realised that, unlike HEE beams with energies below 50 MeV, VHEE beams in the energy range of about 50 to 250 MeV have ballistic properties that make them suitable for treating deep-seated targets (>5 cm), see Fig. 1 and Fig. 2. Furthermore, several aspects related to delivery technology render VHEE beams an attractive candidate modality for FLASH RT. With current technology, small-sized VHEE beams can be readily produced and scanned at UHDR, and VHEE accelerators and gantries are more compact and cheaper than current proton beam technology [5,23,62,63]. While to date there are no clinical VHEE RT devices, interest in creating such devices has seen a resurgence [5,23,62,63], taking on the challenges of designing and building clinical UHDR VHEE RT devices for FLASH RT [64–68]. In the

Table 1
Overview over HEE and VHEE treatment planning studies, related treatment planning tools, and modelled UHDR electron RT devices.

a) HEE RT

References	TPS and/or dose engine	Beam energy [MeV]	RT device	RT technique	Clinical indication/ Treatment sites	FLASH specific considerations
[57]	Elekta XiO[(k)]	4.5, 6	Kinetron, Oriatron eRT6	SBB, PM	Feline nasal planum, porcine skin	Yes
[29,48]	GMV radiance® IORT Planning System/ Eclipse + EGSnrc	4, 6, 9, 12	Mobetron	SBB, PM	N/A	No
[131,132]	Varian Eclipse using eMC + GAMOS MC toolkit (Geant4)	10	2100C/D	SBB, PM	Canine Oral Melanoma, Huma Rib Metastasis	Yes
[16]	RayStation using VMC++-based MC [(a)]	6	Oriatron eRT6	SBB, PM	Feline nasal planum	Yes
[49]	Sordina IORT ECHO TPS using fast MC	6, 8, 10, 12	LIAC FLASH	SBB, PM	N/A	No
[133]	Varian Eclipse using eMC [(a)] (FLEX TPS)	16	TrueBeam, Trilogy	SBB, PM	N/A	Yes

b) VHEE RT

References	TPS and/or dose engine	Beam energy [MeV]	Beam portals	RT technique	Clinical indication/ Treatment sites	FLASH specific considerations
[40,59,60]	In-house pencil beam model + optimizer[(h)]	15–100[(d)]	2–4	IM	Astrocytoma, sacral chordoma, cervical, bladder, pancreas, breast	No
[94]	PENELOPE + in-house optimizer[(h)]	250	5–11	IM	Prostate	No
[61]	PENELOPE + in-house optimizer[(h)]	50–250[(d)]	2–25, 72[(c)]	IM	Prostate	No
[95]	GEANT4 + in-house optimizer	150, 250	7	IM	Prostate	No
[77,134,135]	PENELOPE + in-house optimizer	200 (150–250)	6,8	3D-CRT	Lung, prostate	No
[70]	EGSnrc + RayStation[(a)(i)]	60–120	13, 17, 36	IM	Lung, prostate, paediatric brain tumour	Yes[(e)]
[71]	EGSnrc + RayStation[(a)(i)]	100, 120	16, 32	IM	acoustic neuroma, liver, lung, esophagus, anal	Yes[(e)]
[72]	EGSnrc + RayStation[(a)(i)]	100, 200	16	IM	Prostate, lung, paediatric brain tumour, head and neck	Yes[(e)]
[65]	EGSnrc[(j)]	40	2	3D-CRT	Paediatric whole brain	Yes[(e)(f)]
[69]	RayStation [(a)(b)] using VMC++-based MC [24]	100, 200	3,5,7,16	3D-CRT[(b)]	Glioblastoma, lung, prostate	Yes[(f)]
[96]	FLUKA + in-house optimizer	70, 70–130[(d)]	5–7	IM	Prostate	Yes[(g)]

(a) Research version, (b) Extension to scanned pencil beam scanning in progress, (c) Emulating arc therapy, (d) Energy modulation (multiple energies per beam portal), (e) Dose rates of about 117 Gy/s and short delivery times estimated without further specifications [64,70], (f) 3D-CRT treatments using a few VHEE beams and fixed beam lines can be achieved in short time scales compatible with the FLASH effect [23,62,65,66], (g) Assuming a protection of all organs-at-risk and healthy tissues by a dose-modifying factor of 1, 0.9, 0.8, 0.7, and 0.6, (h) Using partially 2D anatomies, (i) For PHASER project [64], (j) For "scaled-down" PHASER project. (k) Dose engine was not reported.
3D-CRT: 3D conformal RT, IM: intensity modulation technique (also including scanned beams), SBB: single broad beam, PM: Passive modulation, MC: Monte Carlo dose engine.
b) VHEE RT simulation studies and treatment planning tools.

absence of existing VHEE RT devices, UHDR VHEE treatment planning and beam modelling was so far focused on predicting VHEE dose distributions and temporal beam delivery characteristics to assist the design and optimization of future VHEE RT devices and to compare them with standard-of-care RT.

Challenges for UHDR delivery of VHEE RT and contributions of treatment planning

While it was demonstrated *in silico* that scanned VHEE beams can provide a dosimetric plan quality and conformity competitive or even superior to state-of-the-art IMRT techniques (see later), this achievable dosimetric plan quality may be compromised for future UHDR VHEE RT devices, in order to meet temporal dose delivery criteria that optimise the FLASH effect. The investigated delivery concepts for UHDR VHEE RT reach from 3D conformal delivery using a few fixed-beam portals [65,69] to intensity modulated delivery of 0.1–5 mm beamlets from 13 or more fixed-beam portals [64,70–72], see Table 1 **b)**. Technological aspects of UHDR VHEE RT delivery were recently reviewed elsewhere [23,62]. Principal trade-offs to be assessed and optimised by UHDR VHEE treatment planning are dosimetric target coverage and conformity, and temporal dose delivery aspects that optimise the FLASH effect. Ultimately, the best UHDR VHEE RT device design will depend on dependencies of the FLASH effect that are currently not well understood and quantified (see next section). In particular, large doses above 5–10 Gy needed to be delivered within some 100 ms in a given tissue region by experiments to date to trigger and optimise the FLASH effect [73,74]. Current C-arm gantry concepts with rotation speeds of the scale of a minute may therefore no longer be applicable and fixed beam lines or motionless or fast-rotating gantries may become mandatory [62,64,65,75]. However, despite substantial prevailing uncertainties in the knowledge and modelling of the FLASH effect, treatment planning studies are already now useful in evaluating feasibility of UHDR VHEE device configurations. For instance, it was shown that the delivery of only a few 3D-conformal VHEE portals can result in an acceptable dosimetric conformity for clinical indications with simple target geometries, such as whole brain irradiations and glioblastomas [65,66,69], see Fig. 5. This may lower the technological burden for the initial clinical exploration of UHDR VHEE RT, while enabling a quasi-instantaneous fraction delivery. Treatment planning for multi-portal intensity modulated UHDR VHEE RT devices will need to take into account and optimise temporal dose delivery to maximise the FLASH effect.

Beam models of VHEE RT

For the design and assessment of novel VHEE RT devices, the primary requirement for VHEE beam models is to provide realistic predictions of dose distributions produced by VHEE beams in patient anatomies and water phantoms. All recent VHEE treatment planning studies used beam modelling based on the MC technique, see Table 1 **b)**. Fast MC dose engines are the *de facto* standard for

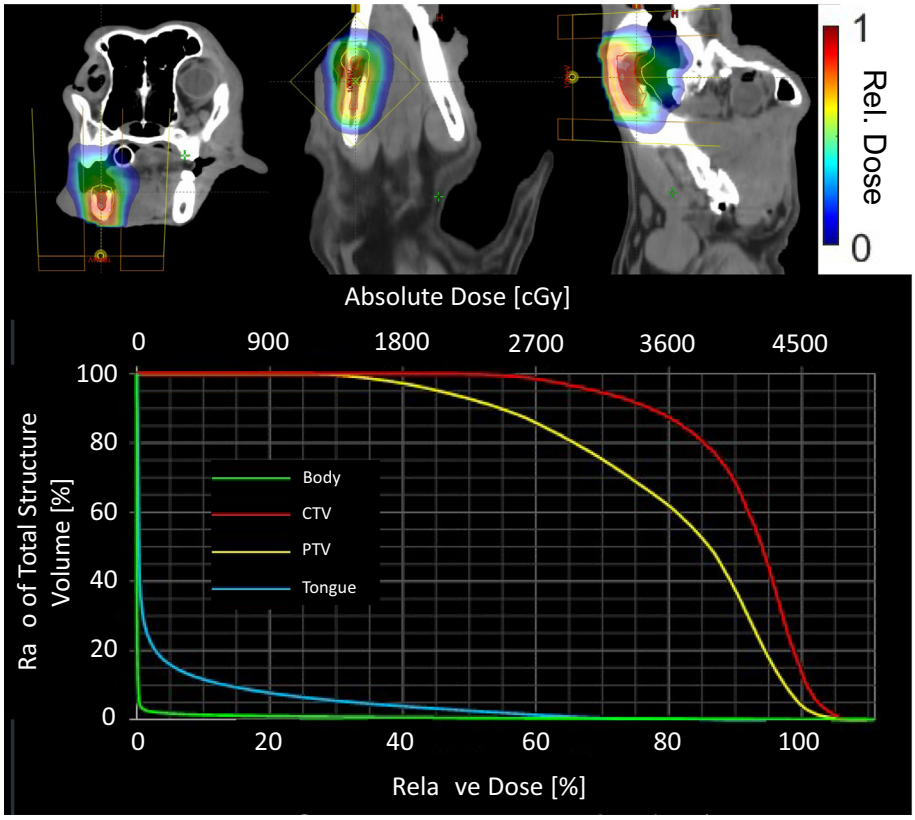

Fig. 4. Example treatment plan for a canine treated for an oral carcinoma [131].

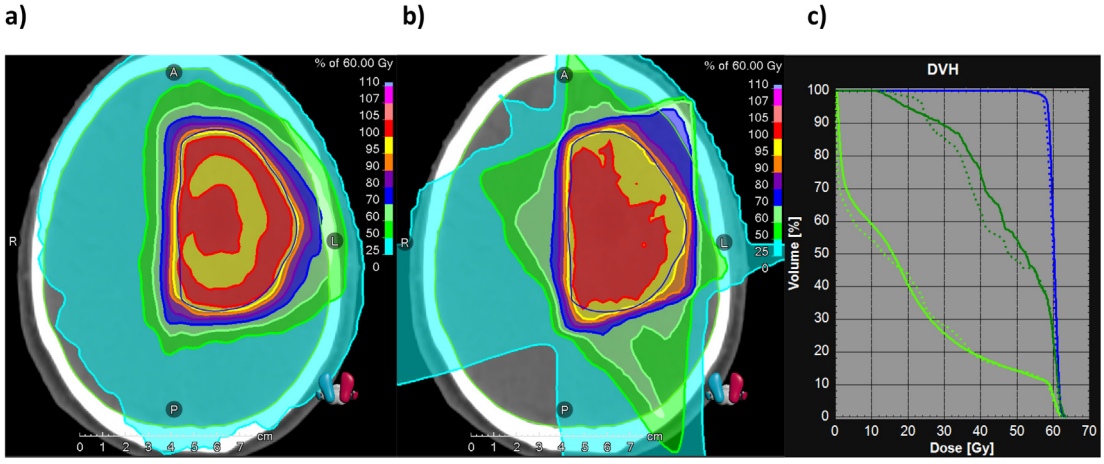

Fig. 5. Treatment planning comparison for a glioblastoma case. 2D dose distributions of **a)** a clinically-approved helical tomotherapy plan and **b)** a 3D-conformal VHEE RT plan using five coplanar VHEE beams of 200 MeV. **c)** Dose-volume histograms (DVH) of the PTV (blue), the brain (light green), and the ventricles (dark green) for the VHEE plans (dotted lines) and the helical therapy plan (solid lines). The comparison illustrates that 3D-conformal VHEE RT using only a few beams can provide plans of similar dosimetric quality as standard-of-care for selected clinical indications with simple target geometries [24,65,69].

HEE RT for commercial TPS, due to improved dose calculation accuracy in heterogeneous tissues regions and irregular surfaces compared to analytical beam model algorithms, as previously mentioned [55]. The physics processes governing particle transport and dose deposition for higher energy electron beams of 50–250 MeV are often simpler than those of lower energy electrons [76] and well modelled by state-of-the-art MC codes [55,77–80]. However, some quantitative uncertainties persist for cross sections and basic physics quantities at such energies. For instance, uncertainties for radiative stopping powers are estimated to be 2% above 50 MeV [76]. Ultimately, VHEE beam models should be validated following standard TPS beam model commissioning procedures, much similar to those established for clinical electron and photon linacs [55,81]. In the absence of VHEE accelerators with clinical beam characteristics, current MC validations are restricted to comparisons of PDD curves and lateral beam sizes produced by millimetre-sized VHEE beams at experimental VHEE facilities in (mostly) water-like materials [22,24,82–88]. Nevertheless, these

studies attest that MC codes are sufficiently accurate for explorative VHEE treatment planning studies.

Dosimetric characteristics of VHEE beams for RT and VHEE treatment planning

So far, the main contribution of VHEE beam modelling and treatment planning studies was to assess and compare the performance and potential of VHEE beams in terms of achievable dose distributions in a therapeutic context. Basic VHEE beam and dosimetric properties are pivotal for this and will be summarised in the following together with the main findings from VHEE treatment planning studies. The PDD and the lateral penumbra of a beam determine the dosimetric conformity, which can be reached in principle by a beam modality. The PDD high dose plateau region (>90% of the maximum) of parallel or nearly-parallel (SSD > 100 cm) VHEE beams can cover depths of typical clinical targets (up to about 20 cm) already with a single beam [24], as illustrated in Fig. 1**, a)**. Compared with clinically-used MV photon beams, the lateral penumbra of HEE beams increases more for increasing depth due to multiple Coulomb scattering and may deteriorate the treatment plan conformity. By increasing the electron beam energy to 50 MeV and beyond, the lateral penumbra can be substantially reduced and can even be smaller than those of clinically-used MV photon beams for lower depths [22,24,58], see Fig. 1**, b)**. Air scattering is substantially reduced when shifting to VHEE energies compared to HEE [50,89]. In fact, for larger depths in water (>5 cm), the lateral penumbrae are essentially driven by multiple Coulomb scattering and are hardly dependent on the air gap. Nevertheless, air gaps below 70 cm are preferable in order to have a small impact on the achievable beam penumbra for superficial targets for VHEE beams below 200 MeV [22]. Finite source size, non-uniform fluences, and scatter from treatment head elements, such as collimation devices, are other factors that may increase the lateral penumbra and that should be accounted for [90–92]. Compared to HEE, MV photon RT and proton therapy (PT), VHEE beams have the advantage that their resulting dose distributions are relatively insensitive to oblique incidences, tissue heterogeneities, anatomic changes, and density uncertainties [58,82,83,91,93].

Multiple explorative treatment planning studies showed that the basic dosimetric VHEE beam properties described above allow to match or outperform dose distributions achieved by state-of-the-art intensity modulated MV photon RT (IMRT) techniques, such as volumetric arc therapy, but are generally inferior to dose distributions achieved by pencil beam scanned proton therapy (IMPT) [61,70–72,94–96]. Table 1 **b)** provides an overview of published VHEE treatment planning studies. Studies focussed predominantly on intensity modulated VHEE treatments of prostate and lung cancers, but encompassed also various other target sites and 3D-conformal delivery techniques. Their main findings on dosimetric plan quality of VHEE RT can be summarised as follows:

- While target coverage and homogeneity is generally comparable to that of IMRT and IMPT techniques, VHEE RT may provide a better sparing of critical organs and lower mean body doses (≈10-30%) compared to IMRT, but spares organs less than IMPT [70–72,94–96].
- VHEE energies of 100 MeV and higher were generally desirable, especially for deep-seated targets, such as the prostate, to improve treatment conformity compared to lower VHEE energies [24,61,70,72,95].
- Using energy-modulation with three VHEE beam energies per beam portal (e.g., 50, 150, 250 MeV) may result in slightly improved plans, but (unlike protons) using a finer energy-modulation does not result in further plan improvement (due to a relatively mild variation of the PDD as a function of energy) [61].
- Using few-beam (2–7) 3D conformal delivery techniques may result in acceptable dose distributions for clinical indications with simple target geometries [65,69], see Fig. 5.

Limitations of these studies include the assumption of hypothetical and mostly idealised VHEE device designs and beam parameters that may be difficult to realise. Furthermore, most of the studies use only a small number of patient cases and are prone to planners' biases.

Using magnetic quadrupole focussing, convergent VHEE beams can be obtained and were shown to result in strongly peaked PDD thereby allowing to cover small volumes (0.1–1 cm^3) at a selected depth with conformal dose distributions [97,98], see Fig. 1**,** and a superposition of several of such focussed VHEE beams in depth was shown to create 'spread-out electron peaks' [68]. While this delivery concept is in principle appealing for treatment planning of small stereotactic targets, as it results for small volumes of a few cm^3 in depths-dose distributions with a conformity similar to the one achieved by particle therapy, it comes with some conceptual and technical challenges that may render it impractical when applying it to larger target volumes. In particular, conformity in depth will be lost when scanned target areas are on the scale of the beam extension before focussing, due to dose superposition effects before and after the focal spot (see **Supplementary** Fig. 1 for details) and the technical feasibility of scanning a broad beam (>15 cm) precisely over a large tumour volume yet remains to be shown. An alternative use of magnets for enhancing VHEE beam characteristics for RT is the application of a strong magnetic field in beam direction, since the spiralling motion for scattered electrons induced by the Lorentz force will then sharpen the lateral beam penumbra. This was already proposed in 1949 for 20 and 50 MeV beams [99]. Since then, this concept has been investigated in more detail by simulations and experiments for HEE beams [100–106], but may be equally applied to higher energy electron beams to result in a sharper penumbra, thus offsetting one of the principal shortcomings of electron beams for RT and allowing thereby to use lower VHEE beam energies (see **Supplementary** Fig. 2 for details). Delivery techniques employing magnetic fields will require novel dedicated treatment planning tools for the assessment of their feasibility and clinical potential.

Accounting for the FLASH effect in UHDR electron treatment planning

While absorbed dose will likely remain a mainstay in prescribing and evaluating UHDR RT, it may no longer be a sufficient predictor of clinical outcome for UHDR electron beam treatments that result in a substantial FLASH effect. Being able to quantitatively assess the FLASH effect in the planning phase, ideally integrated with the evaluation of conventional dosimetric effects, may be desirable to achieve the ultimate goal of an optimised therapeutic ratio. Accounting for the FLASH effect in treatment planning is currently exacerbated by both the lack of an established mechanistic understanding and limited experimental characterization of the FLASH effect. At the time of writing, there was no commonly accepted and validated mechanistic explanation of the FLASH effect [2–4,107]. Furthermore, the dose delivery and biological conditions for achieving the FLASH effect are not precisely understood. Current experimental evidence for irradiation parameter requirements can be summarised as follows. UHDR irradiations using single broad electrons beams were able to produce a pronounced FLASH effect when delivering a large doses (>4–

Table 2
TPS physics beam model parameters with recommended accuracy for electron UHDR RT.

Parameters	Definition	Beam model specification	Typical Range	Recommended accuracy (std/mean)
Pulse repition rate	Number of pulses per second	Per irradiator for all UHDR modes	10–360 Hz	1%
Duty cycle	Ratio of pulse ON time to OFF time	Per irradiator for all UHDR modes	1/2000–1/100	1%
Temporal pulse structure	Temporal sequence of radiation pulses from the beginning to end of delviery, including the ramp-up	User-defined reference point or plane	NA	5%
Dose per pulse	D_p	User-defined reference point or plane	0.1–10 Gy	5%
Intra-pulse dose rate	$\dot{D}_p = dD_p/dt$	User-defined reference point or plane	10^4–10^6 Gy/sec	5%
Time-averaged dose rate per beam	$\bar{\dot{D}} = \int_0^{t_0} \dot{D}_p dt/t_0$ for each beam	User-defined reference point or plane	50–3000 Gy/sec	5%
Time-averaged dose rate per fraction	$\bar{\dot{D}} = \int_0^{t_0} \dot{D}_p dt/t_0$ for each fraction	User-defined reference point or plane	delivery specific	5%
Scanning pattern	Temporal sequence of the scanning beam	Treatment volume	delivery specific	1%
Volumetric dose rate distribution per beam and per fraction	Temporal dose distribution for each voxel in the treatment volume. In the case of a scanning beam, spatiotemporal dynamics introduced by the scanning pattern and temporal pulse structure need to be modelled.	Treatment volume	delivery specific	5%

8 Gy) in a short overall delivery duration (<200 ms) and currently available single fraction data suggest that the FLASH effect is diminished or lost when decreasing the dose per fraction or prolonging the treatment time [3,74,108–111]. Instead, for increasing single fraction doses, *in vivo* data show a trend towards an increased normal tissue protection [3,74,112,113]. It is currently unclear how pauses in dose delivery between fields and scans impact the achieved FLASH effect. Albeit understanding this behaviour may be pivotal for the UHDR device design and the associated treatment delivery technique. Proposed dose delivery parameters of possible importance for enabling and optimising the FLASH effect may include dose(-per-fraction), dose delivery duration, time-averaged dose rate (TADR), intra-pulse dose rate (IPDR), dose per pulse (DPP) and others [3–5,114,115] (see Table 2). Since, to date, most experimental data comes from large single fraction doses, there is also little experimental evidence on the behaviour of the FLASH effect for fractionated treatments. While a recent study could demonstrate a reduced toxicity to the mice brain for fractionated UHDR irradiations, it is difficult to extract any quantitative information on the behaviour from the study [116]. Last, the effect magnitude is not known for biological systems and endpoints of relevance for the clinics.

Different approaches have been pursued or lend themselves to account for the FLASH effect quantitatively in treatment planning. Hereafter, we will refer to them as 'FLASH predictors' and categorise them into three groups.

- Various dose delivery parameter-based metrics that aim to quantify the 'FLASH potential' of a dose distribution have been proposed. They include simple parameter thresholds, such as dose, dose rate and dose rate volume histogram thresholds and aim typically to quantify voxels or a dose fraction per voxel that fulfil these criteria, assuming a binary FLASH effect [114,117–120]. Furthermore, more complex metrics, such as dose-averaged dose rate and '95% of the dose in a voxel delivered within a certain time', have been proposed for UHDR treatments with a more complex delivery time structure, such as scanned beams delivered via multiple portals [75,114,118,121–123]. While latter metrics have been developed in the context of UHDR PT, they could be equally applied to UHDR electron beam RT. Analogous to a voxel-based relative biological effectiveness weighting factor for dose, as it is used for decades for clinical carbon ion therapy [124], UHDR doses can be weighted by a voxel-based dose-modifying factor (DMF= $(D_{UHDR}/D_{CONV})|_{isoeffect}$, where D_{UHDR}, resp. D_{CONV}, is the dose delivered in UHDR mode, resp. in CONV mode, for an iso-effect to the tissue) [74,75,119,122,125]. This has been used by some treatment planning studies either using generic DMF factors [96,119,122,126] or utilising a modelling based on the radiolytic oxygen depletion hypothesis [75].
- A direct prediction of TCP/NTCP for a given UHDR plan is also an option for the quantification of the FLASH effect for treatment planning, but has, to our knowledge, not yet been applied in UHDR treatment planning studies.

FLASH predictors may also be built into cost functions for the optimization of UHDR treatment plans [75,122].

FLASH predictors used by current treatment planning studies are often simplistic and the more complex ones are often not sufficiently backed by experimental evidence. Hence, care should be taken when interpreting results based on such FLASH predictors [73,127]. At the time of writing, no consensus has been reached on the use of FLASH predictors for treatment planning and findings of current and future preclinical studies and clinical trials conducted under various biological and irradiation conditions need be distilled to establish commonly accepted FLASH predictors for treatment planning. In the meantime, dosimetric and beam parameters of particular interest such as pulse structure should be defined in the TPS so that FLASH predictors can be computed and are reportable. Note that for a 3D-conformed UHDR delivery consisting of static beams, the temporal dose delivery is defined and can be recorded and reported by the 3D dose distribution per beam (e.g. DICOM RT DOSE) plus the knowledge of the temporal beam delivery structure. Among studies utilising UHDR electron beams, where dedicated accelerators or converted medical linacs have been primarily used, large variations in the temporal pulse structure (ramp-up, IPDR, DPP, pulse width/duration, pulse repetition frequency and TADR) have been reported [107,128]. To assist the cross-platform interpretation of outcomes and to reproduce the irradiation when necessary, the definition, recording and reporting

of the aforementioned parameters (Table 2) in the TPS are highly recommended [129]. Indeed, the standardisation remains challenging due to significant varieties across platforms. The pulse structure should be at least reportable at a user-defined point in the treatment plan, like the dose calculation point in conventional RT plans.

Conclusion

Treatment planning and beam modelling of UHDR electron beams is currently in its initial stage of development and there has been little use of treatment planning so far in initial veterinary and human UHDR electron treatments. Published UHDR treatment planning studies for HEE and VHEE beams focus predominantly on dosimetric aspects with no or at best very simplistic considerations of the FLASH effect. However, UHDR electron beam treatment planning can be expected to play a key role for an optimised clinical transfer of electron beam FLASH RT and UHDR device design to treat more complex clinical indications and to optimise its dosimetric conformity and therapeutic ratio. Furthermore, it will be important for *in silico* evaluations of the performance of VHEE beam FLASH RT in comparison to state-of-the-art CONV RT and other FLASH RT modalities, such as protons. A quantitative and accurate modelling of the FLASH effect in UHDR treatment planning is one of the main challenges to tackle for its usefulness, but awaits advancements in experimental characterizations of the FLASH effect and, possibly, its mechanistic understanding.

Conflict of interest statement

RM and TTB have a research collaboration with RaySearch Labs. The other authors have nothing to disclose.

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Appendix A. Supplementary material

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