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Original Article

Very high-energy electron therapy as light-particle alternative to transmission proton FLASH therapy – An evaluation of dosimetric performances

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ABSTRACT

Purpose: Clinical translation of FLASH-radiotherapy (RT) to deep-seated tumours is still a technological challenge. One proposed solution consists of using ultra-high dose rate transmission proton (TP) beams of about 200–250 MeV to irradiate the tumour with the flat entrance of the proton depth-dose profile. This work evaluates the dosimetric performance of very high-energy electron (VHEE)-based RT (50–250 MeV) as a potential alternative to TP-based RT for the clinical transfer of the FLASH effect.

Methods: Basic physics characteristics of VHEE and TP beams were compared utilizing Monte Carlo simulations in water. A VHEE-enabled research treatment planning system was used to evaluate the plan quality achievable with VHEE beams of different energies, compared to 250 MeV TP beams for a glioblastoma, an oesophagus, and a prostate cancer case.

Results: Like TP, VHEE above 100 MeV can treat targets with roughly flat (within ± 20 %) depth-dose distributions. The achievable dosimetric target conformity and adjacent organs-at-risk (OAR) sparing is consequently driven for both modalities by their lateral beam penumbrae. Electron beams of 400[500] MeV match the penumbra of 200[250] MeV TP beams and penumbra is increased for lower electron energies. For the investigated patient cases, VHEE plans with energies of 150 MeV and above achieved a dosimetric plan quality comparable to that of 250 MeV TP plans. For the glioblastoma and the oesophagus case, although having a decreased conformity, even 100 MeV VHEE plans provided a similar target coverage and OAR sparing compared to TP.

Conclusions: VHEE-based FLASH-RT using sufficiently high beam energies may provide a lighter-particle alternative to TP-based FLASH-RT with comparable dosimetric plan quality.

Introduction

FLASH-radiotherapy (RT) delivered on sub-second time scales with ultra-high dose rates (UHDR) has been shown to produce normal tissue sparing while retaining tumour efficacy (so called "FLASH effect") in preclinical settings [1–4]. Clinical translation of FLASH-RT to deep-seated tumours is still a technological challenge [5–7]. One frequently promoted solution consists of utilizing pencil beam scanned (PBS) proton beams with an energy of about 200–250 MeV to irradiate the tumour with the flat entrance of the proton depth-dose profile, so-called transmission proton (TP) beams [8,9]. This treatment modality lends itself for the extension of FLASH-RT to deep-seated targets, since such proton pencil beams can be produced at UHDR by upgrading existing proton therapy technology [5,6]. Recent treatment planning studies advocate the use of TP-based FLASH-RT and find comparable or slightly superior dosimetric plan quality (without FLASH effect) compared to state-of-the-art photon therapy [9–15].

Electron beams of 50–250 MeV – very high-energy electrons (VHEE) – have sufficient penetration to treat lesions at typical clinical depths and lateral beam penumbrae that may be comparable with those of

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state-of-the-art MV photon RT [16,17]. Multiple treatment planning studies investigating VHEE therapy (without FLASH effect) found that VHEE may provide treatment plans that are generally superior to those achieved by volumetric modulated arc therapy, but inferior to plans using proton therapy [18–21]. VHEE beams may be readily produced at UHDR rates and there are several recent initiatives that design and built clinical VHEE-based FLASH-RT devices [5,7,22–28]. VHEE can be accelerated and steered, much like protons. However, due to a charge-mass ratio increased by a factor of about 1800, VHEE technology has the potential to provide a smaller technological footprint compared to clinical proton therapy units [7,22–25,29]. The objective of this work is to compare the dosimetric performances of VHEE-based treatments to TP-based treatments to assess their potential for FLASH-RT.

Materials and Methods

Monte Carlo simulations in water phantoms

With the aim to compare and evaluate principal dosimetric properties of VHEE and TP beams that define their respective clinical applicability and performance, we performed Monte Carlo simulation with the FLUKA code [30–32] (4–1.1 and 2023.3). Simulations were conducted using the 'PRECISIOn' setting and the new evaporation model. FLUKA has been extensively validated for clinical proton beams [33] and was shown to reproduce also measurements of VHEE beams [34,35]. We simulated proton beams of 200–250 MeV and electron beams of 50–250 MeV impinging on a water phantom (30 x 30 x 50 cm^3) without and with air gaps of 50 and 100 cm. To illustrate the behaviour of VHEE beams beyond an energy range up to 250 MeV (mostly discussed for clinical applications [7]), we additionally simulated electron beams of 400 and 500 MeV. Simulations were performed for parallel Gaussian pencil beams with full-width at half-maximum (FWHM) of 5 and 10 mm (lower limit of what is commonly used by clinical cyclotron-based PBS proton therapy [33,36–38], for synchrotron-based systems beams down to 2 mm have been reached [38]), as well as for broad circular beams with diameter of 10 cm at the phantom surface. Beam size was defined at the beam source position, which was either at the entrance of the water phantom or at the distance given by the respective air gap. Percentage depth-dose (PDD) were scored with a 1 mm binning in depth. Lateral profiles were scored using a 1 mm binning at 0, 5, 10, 15, 20, and 30 cm depth. The lateral penumbra was calculated as the distance between 80 % and 20 % of the maximum dose. We simulated only parallel VHEE beams since the dependence of the lateral penumbra on the beam divergence is generally small [17]. Simulations were performed using 20 million primary particles. They allow to compare typical depth-dose distributions and achievable penumbrae for both beam modalities for idealized situations.

Treatment planning of patient cases

A research version of the treatment planning system RayStation (RayStation 12A DTK, RaySearch Laboratories, Sweden) [39] was used for treatment planning with TP and VHEE beams. Plan creation, optimization, and evaluation were conducted using RayStation's user interface and its Python-based scripting interface. PBS proton dose computation and treatment planning with RayStation is clinically well established and validated [39,40]. VHEE treatment planning uses the PBS proton plan creation and optimization functionalities with a newly developed dose engine for computing VHEE pencil beam dose distributions. To assure the accuracy of the physics modelling of the newly developed code, it was validated against general-purpose Monte Carlo codes, see Supplementary Figs. 1 and 2.

We evaluated dosimetric differences on the plan level resulting from differences between VHEE and TP on a glioblastoma, an oesophagus, and a localized prostate cancer patient case contoured according to established guidelines [41–43]. This selection encompasses tumours at different depths and treatment sites in the body (Table 1). To avoid potential biases in the dosimetric evaluation of both techniques due to differences in the planning approach, we created TP and VHEE treatments plans using identical plan configurations except for the particle type and beam energy, as well as using the same optimization objectives. In detail, treatment plans for both modalities were computed for Gaussian pencil beams of 5 mm FWHM with zero angular spread and divergence at a virtual source plane 1 m upstream from the spot position in the isocentre plane. Mean direction of a spot with respect to the field direction was determined by a focal length [39] of 250 cm (i.e., the virtual source-axis distance for pencil beam deflection), a typical value for clinical proton therapy systems [37]. For VHEE, Monte Carlo dose computations were performed taking into account scattering in air between the virtual source plane and the patient. For 250 MeV TP, scattering in air is small (see Results section) and simulations were performed assuming vacuum between the virtual source plane and the patient [39]. Patient plans were generated using seven co-planar fields with equiangular spacing. For pencil beam scanning, a hexagonal grid with a spot spacing of 1σ of the spot size was used to cover the target. Such a spacing may provide a homogeneous and dense target coverage [44]. Using these settings, we created plans either using proton pencil beams of 250 MeV or electron pencil beams with energies between 50 and 250 MeV.

TP plan optimization and evaluation was conducted following institutional prescriptions and using clinical goals based on RTOG and QUANTEC [45]. We used then the same objectives and constraints for the optimization of the VHEE plans, thereby reducing risk for a possible operator's bias in the results. Plan quality was compared based on absorbed dose distributions, dose-volume histograms (DVH) and dose metrics. For the planning target volumes (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 organs-at-risk (OAR), we evaluated $D_{2\%}$, D_{mean} and other organ-specific metrics, and compared them against our institutional clinical planning goals.

Results

PDDs of 10-cm-diameter proton and electron beams of different energies are shown in Fig. 1 **(a)**. PDDs of both TP and VHEE beams of 100 MeV and above are within ± 20 % over 20 cm depth and have a similar ascending slope. For proton beams of 200 [225, 250] MeV, parts or the entire Bragg peak dose is deposited in the patient if the beam needs to cross more than ~ 22 [28, 35] cm of water-equivalent tissues. This discourages the utilization of TP for certain treatment sites and incident angles if their energy is not sufficiently high. Fig. 1 **(b,c)** shows a comparison of the lateral penumbrae as a function of depth in water obtained for single parallel Gaussian proton and electron beams with a FWHM of 5 and 10 mm for the case where the beam particle source is defined at the surface of the water phantom. Penumbrae are driven for both modalities by multiple Coulomb scattering in water. 400 [500] MeV electron beams match the penumbra of 200 [250] MeV TP beams

Table 1
Overview of some of the key plan characteristics.

Case	PTV size (cm^3)	Isocentre depth range* (cm)	Prescribed dose (Gy)	Fractions
Glioblastoma	197	4.2–13.6	39.9	15
Oesophagus cancer	104	8.7–18.7#	60	30
Prostate cancer	110	10.0–18.6	78	39

* The range was determined by measuring the minimum and the maximum distance between the patient outline and the centre of the PTV. # Low density lung tissue contributes to this depth thereby decreasing the effective water-equivalent depth of the isocentre.

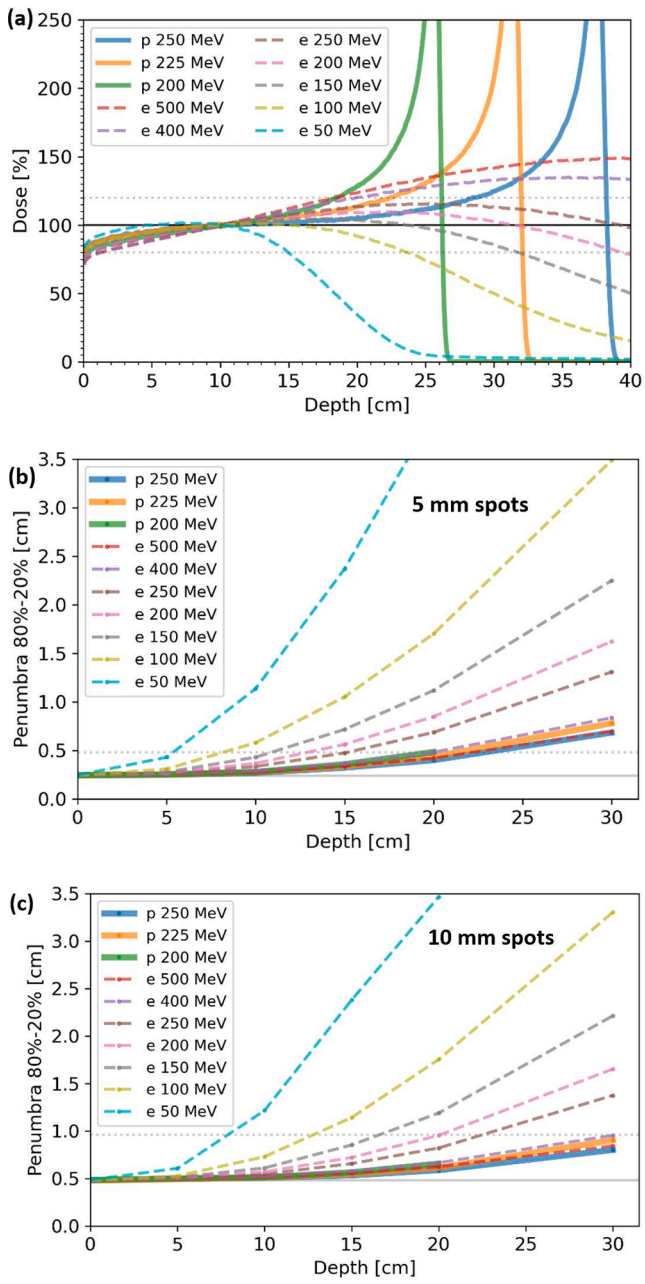

Fig. 1. (a) Central-axis percentage depth-dose (PDD) profiles in water of parallel 10-cm-diameter proton and very high-energy electron (VHEE) beams of different energies. Profiles are normalized on the central axis at a reference depth of 10 cm. Horizontal dotted lines indicate ± 20 % of the dose at the reference depth. Lateral 80 %-20 % penumbra of single parallel Gaussian proton and VHEE beams with a FWHM of 5 mm **(b)** and 10 mm **(c)** in water (without air gap). Horizontal solid and dotted lines indicate 100 % and 200 % of the initial beam penumbra, respectively.

over the whole evaluated depth range. VHEE beams of 50–250 MeV have a notably increased penumbra compared to 200–250 MeV TP beams for depths larger than 5–10 cm. Differences vary, however, substantially with VHEE energy and depth of clinical interest. Relative differences between penumbrae for depths of clinical interest ($\lesssim$20 cm) are decreased for initial pencil beam sizes larger than 5 mm FWHM, since the penumbrae are determined for such cases to a larger degree by the Gaussian shape of the initial pencil beam size (see relative differences between TP and VHEE beams in Fig. 1 **(b,c)**). For VHEE energies $\lesssim$100 MeV and air gaps before the phantom that exceed 50 cm, scattering in air may substantially increase the lateral penumbrae, especially for shallower depths, see **Supplementary** Fig. 3. In contrast, for beam energies above 150 MeV and air gaps up to 100 cm, scattering in air has only a minor impact on the overall penumbra for VHEE and TP.

Dose distributions and DVHs obtained for the glioblastoma, the oesophagus, and the prostate case are displayed in Fig. 2, Fig. 3, and Fig. 4, respectively, for the 250 MeV TP plans, as well as for the 100 and 200 MeV VHEE plans. Dose distributions and DVHs for TP and all investigated VHEE beam energies are provided for the three patient cases in **Supplementary Figure 4, 5, 6 and 7**. Similar dose distributions, including similar local features, can be observed for the respective TP and VHEE plans. This indicates that the identically posed optimization problem converged to similar solutions for both modalities and, hence, that dosimetric differences between plans can be mostly attributed to dosimetric differences in the respective TP and VHEE beamlets. The corresponding dose metrics are summarized in **Supplementary Table 1**. Except for the 50 MeV VHEE, $V_{95\%}$ was for all plans above 95 % (always within 4 % of the corresponding 250 MeV TP plans) and $HI_{98\%}$ was for all plans above 0.89 (always within 0.04 of the corresponding 250 MeV TP plans). Homogeneity and $HI_{98\%}$ were degraded for 50 MeV VHEE plans, most notably for the oesophagus case. Institutional clinical OAR goals were fulfilled for all TP and VHEE plans. Dosimetric conformity of VHEE plans generally improved for increased energies, as can be seen from the DVHs of the ring structures and the $CI_{50\%}$. For the glioblastoma case that represents a shallower target, a $CI_{50\%}$ within 0.03 of the TP plan could be reached by VHEE plans of 100 MeV and above (**Supplementary Table 1**). Instead, for the oesophagus and the prostate case an energy of 250 MeV was needed to achieve a $CI_{50\%}$ within 0.03. For the glioblastoma and the oesophagus case, albeit having partially reduced dosimetric conformity, 100–250 MeV VHEE plans showed mostly only small differences in DVHs and associated dose metrics for critical OAR (<5% for volume, <2 Gy for dose), see **Supplementary Table 1**. For the prostate case instead, VHEE beam energies of 150 MeV and above were needed to achieve DVHs and dose metrics that were mostly similar or only slightly worse compared to the 250 MeV TP plans. For the prostate cancer case, a proton energy of 250 MeV was insufficient for completely depositing the whole Bragg peak doses outside the patient for two out of seven field directions (see arrows in Fig. 4).

Discussion

Transmission proton and VHEE beams are two of the technologically most evolved and promising beam modalities proposed to be used for FLASH-RT [5–9]. To the best of our knowledge this is the first treatment planning study directly comparing dosimetric performances of VHEE therapy with TP therapy [46]. Simulations in water phantoms from this work (Fig. 1 **(a)**) and others [16,17,33] illustrate that both parallel TP and VHEE beams result in roughly flat PDD. It is therefore the lateral beam penumbrae that will drive the achievable target conformity and adjacent OAR sparing in the high-dose region for both beam modalities. Our simulations show that VHEE beams with energies of 400 [500] MeV match penumbrae of 200 [250] MeV TP beams, whereas VHEE beams of lower energies have larger penumbrae (see Fig. 1 **(b, c)**).

Compared to these idealized scenarios, the impact of the relative differences between dose falloffs achievable with TP beams and VHEE beams of different energies will be substantially reduced for clinical dose distributions by multiple additional factors. These include the spot spacing density and the spot size at isocentre in air, which defines the minimal lateral penumbra. Spot sizes of about 5–20 mm (FWHM) with an associated initial 80 %-20 % penumbrae of 2.4–9.6 mm are used clinically for PBS proton therapy treatments [33,36,37]. A larger spot size with a larger initial penumbra reduces the relative contribution of multiple Coulomb scattering in the phantom/patient to the overall lateral beam penumbra[47]. Thereby it diminishes dosimetric differences between TP and VHEE plans.

Anatomical heterogeneities in the patient, beam directions, and spot

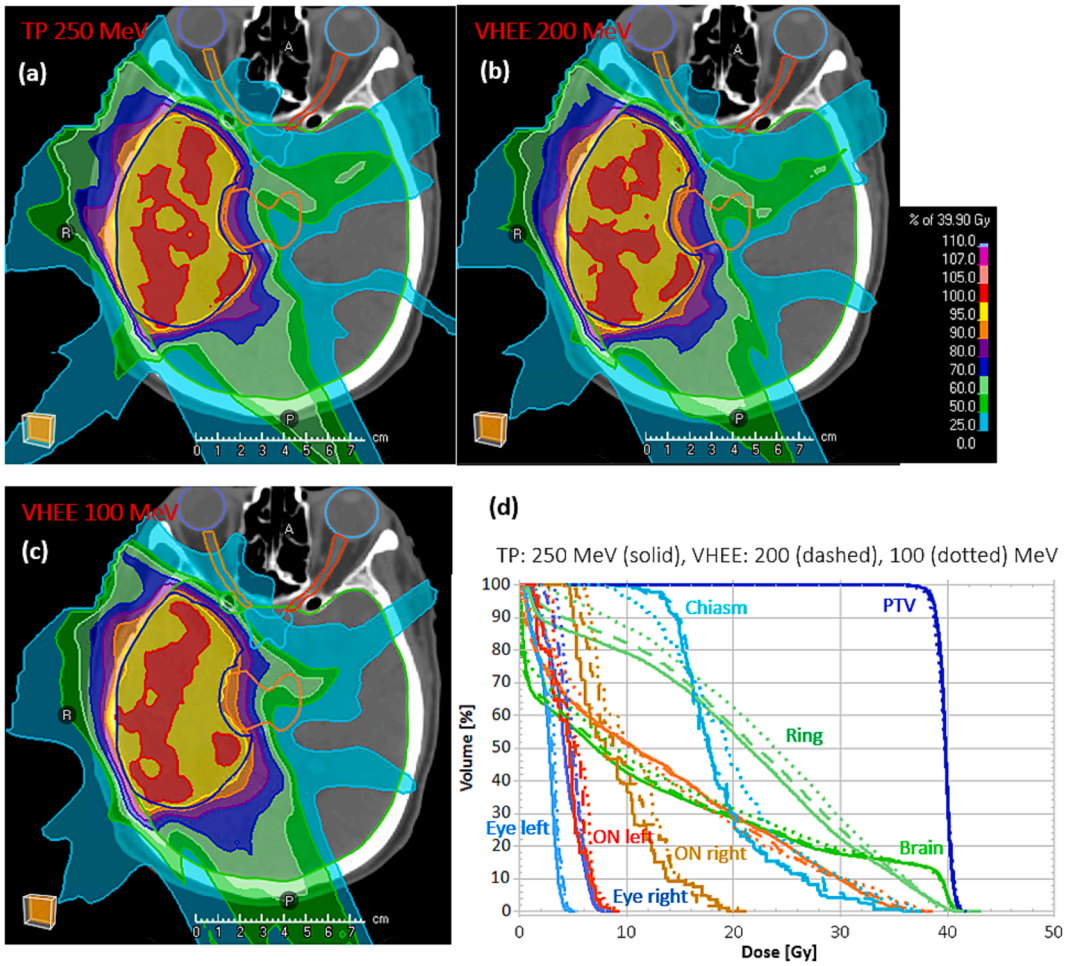

Fig. 2. Axial dose distributions **(a-c)** and dose-volume histograms **(d)** for a glioblastoma case obtained using 250 MeV transmission proton (TP) therapy **(a)**, 200 MeV very high-energy electron (VHEE) therapy **(b)**, and 100 MeV VHEE therapy **(c)**. The ring structure represents a wall of 2 cm extension around the PTV that is cropped to the patient outline. Abbreviations: ON = Optical nerve.

placements are additional plan-specific factors that limit achievable dose falloffs to spare OAR. These factors are captured by our treatment plan comparisons indicating that 150–250 MeV VHEE beams may achieve a dosimetric plan quality comparable to that of 250 MeV TP plans for cranial and thoracic indications and that even VHEE plans using lower beam energies of 100 MeV, although having a decreased conformity, may provide acceptable dose distributions for these sites with very similar OAR DVHs and dose metrics compared to the TP plans. Instead, results for the prostate case demonstrate that deeper-seated targets are preferentially treated using VHEE beams of 150 MeV and above. Lower VHEE beam energies produced large beam penumbra that substantially degraded conformity compared to 250 MeV TP plans. Similar findings were reported by other VHEE treatment planning studies [18,20,48]. Our studies used rather large air gaps to the patient surface (~90 cm), which lead to substantially increased spot sizes for VHEE beams of energies $\lesssim$100 MeV due to scattering in air (see **Supplementary** Fig. 3). Hence, dose distributions of these plans could be further improved by decreasing air gaps. TP treatments need protons with energies larger than those produced by current clinical systems (200–250 MeV) to locate Bragg peaks safely outside the patient for targets in the abdomen and pelvis or may be limited in the available beam directions admitted for irradiation (see Fig. 4 **(a)**).

Spot sizes of 5 mm FWHM, used for the plans presented in this work, are on the lower end of what is reasonable and currently used for clinical proton therapy plans [33,36–38]. Since they result in larger relative penumbra differences between VHEE and TP due to scattering differences in the patient, this represents a worst-case scenario for VHEE beams and tends to emphasize dosimetric differences between the two modalities on the plan level that are due to dosimetric differences on the beamlet level. On the contrary, differences in dosimetric plan quality, which are due to dose differences on the beamlet level between the two modalities, can be expected to be of less importance if less spots of larger sizes and with a larger spacing are used since dose distributions for both modalities will be degraded compared to the ones presented here. In fact, the technical realization of UHDR treatments on sub-second time scales is likely to entail compromises in the achievable dosimetric plan conformity, independent of the particle species and energy. These may include less spots of larger sizes and fewer beam directions [5,10,11,23,26,27,49]. Such compromises may further decrease the importance of potential dosimetric advantages of TP over VHEE beams compared to plan comparisons presented in this study.

A limitation of this study is that it evaluates dosimetric differences between TP and VHEE beams on the patient level only for three patient cases. This allowed us to assess representative dosimetric differences and systematics for the evaluated treatment sites and target depths (see Table 1). Instead, large-sample treatment planning studies will be needed to evaluate average differences in dose metrics and their variations for specific patient cohorts. However, the identical plan configuration and optimization approach chosen in this work for TP and VHEE plans, allowed us to evaluate and highlight systematics of how dosimetric differences on the beamlet level between TP and VHEE translate to the plan level for clinical situations. It demonstrates that, compared to

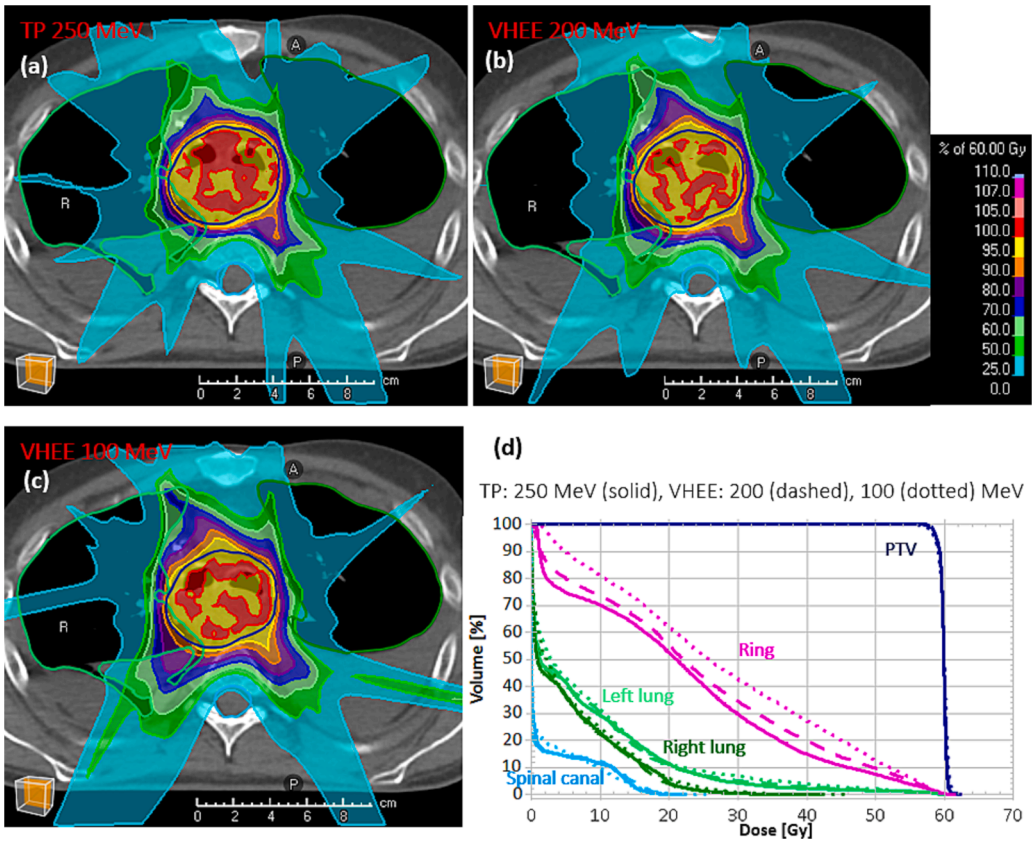

Fig. 3. Axial dose distributions **(a-c)** and dose-volume histograms **(d)** for an oesophagus cancer case obtained using 250 MeV transmission proton (TP) therapy **(a)**, 200 MeV very high-energy electron (VHEE) therapy **(b)**, and 100 MeV VHEE therapy **(c)**. The ring structure represents a wall of 3 cm extension around the PTV.

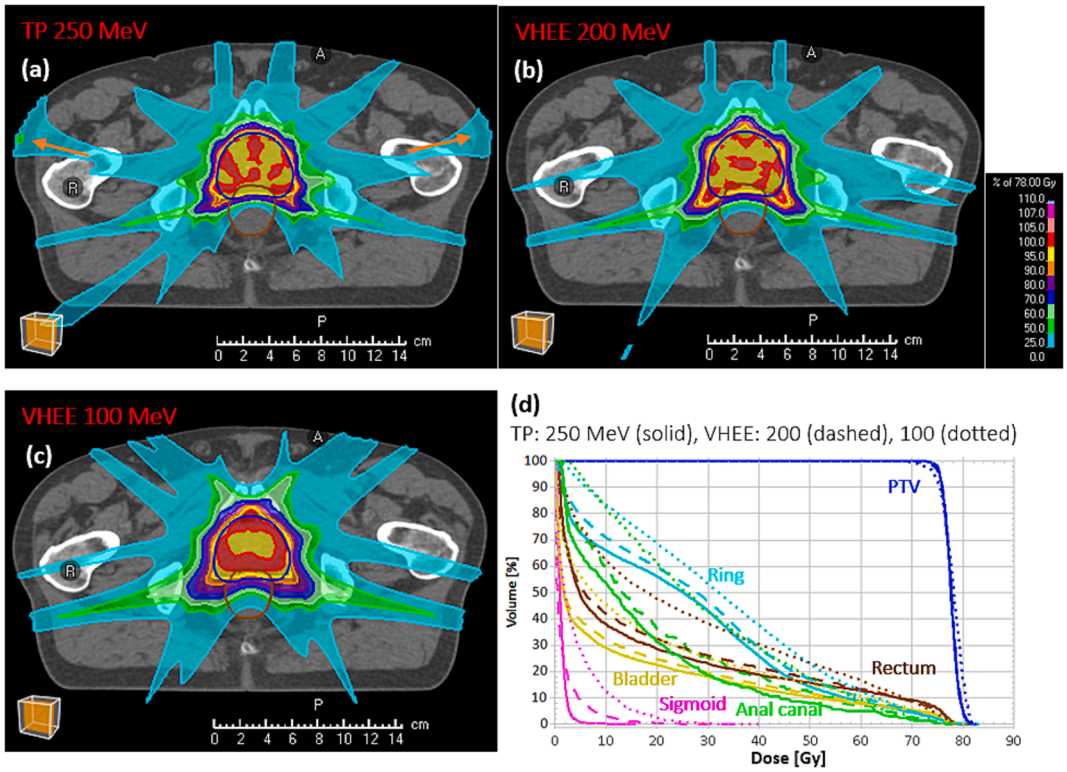

Fig. 4. Axial dose distributions **(a-c)** and dose-volume histograms **(d)** for a prostate cancer case obtained using 250 MeV transmission proton (TP) therapy **(a)**, 200 MeV very high-energy electron (VHEE) therapy **(b)**, and 100 MeV VHEE therapy **(c)**. The ring structure represents a wall of 3 cm extension around the PTV. For the TP plan **(a)**, two arrows indicate the beam directions depositing parts of the Bragg peak doses inside the patient.

250 MeV TP plans, almost identical dose distributions can be obtained for different target sizes and depths by VHEE plans with 150–250 MeV, since beamlet dose distributions (i.e., pencil beams) of both modalities are sufficiently similar. Given identical plan parameter configurations and pencil beam sizes of 5 mm FWHM and larger, this equivalence will persist for other treatment situations for the two modalities. The demonstrated similar dosimetric performance of VHEE therapy and TP therapy also suggests that many of the results obtained by dedicated TP studies for specific treatment indications [9–15] can be transposed to VHEE therapy using sufficiently high energies and similar pencil beam characteristics as in the original TP studies.

It may be worth mentioning that even though a substantial dosimetric benefit has been demonstrated in numerous comparative treatment planning studies for clinical PBS protons with respect to intensity modulated MV photon techniques (mostly for the medium to low dose region), it remains for many indications difficult to show that this dosimetric benefit translates into clinically superior outcomes [54,55]. This experience suggests that the relatively small differences found for absorbed dose distributions of TP and VHEE plans using beams of sufficiently high energies will likely not to result in clinically detectable outcome differences.

Due to the similar pencil beam dose kernels and similar dose gradients, it is expected that both dose distributions of TP plans and VHEE plans of higher energies have a similar robustness against anatomical and set-up changes. Some publications suggest that VHEE and TP treatments may have an increased robustness compared to conventional proton and photon therapy [8,50–52].

Another limitation of this work is that it assumes idealized TP and VHEE pencil beams without contributions from additional particles, as they may be produced in the treatment head. For clinical proton machines, the dosimetric contributions of such particles are generally small and can be taken into account by the dose engine when computing dose distributions in the patient. Similarly, for VHEE beams, neutrons and photons produced in the treatment head are expected to contribute by multiple orders of magnitude less to the central axis dose and the total neutron doses of scanned VHEE was estimated to be 1–2 orders of magnitude smaller than the one for scanned proton beams [53]. Hence, an explicit consideration of such secondary particles can be expected to have little impact on the findings of this work.

While this study does not demonstrate a substantial dosimetric incentive favouring TP-based FLASH-RT treatments over VHEE-based FLASH-RT treatments, there are other technological and potentially biological factors that may be more decisive for favouring one beam modality over the other for FLASH-RT. As initially pointed out, the higher charge-mass ratio of electrons compared to protons may contribute to reduce size and cost of future VHEE-based FLASH-RT devices compared to TP-based FLASH-RT since it eases particle acceleration and steering [5–7]. Recent experimental data suggests that the dose of an UHDR treatment fraction needs to be delivered to tissue with a short overall time (~100 ms) and without pauses between beams for an optimized FLASH sparing effect [56–58]. The reduced magnetic rigidity of VHEE beams compared to TP beams will be particularly appealing in such a case to achieve compact pluri-directional UHDR beam delivery concepts within a short overall delivery time, for instance, by using multiple fixed beam lines [24,27,49] or novel stationary or rotating gantry concepts [5,59,60]. Additionally, a reduced magnetic rigidity may help to improve temporal dose delivery characteristics. Notably, by resulting in faster scanning speeds for the same magnetic field ramping speeds and scanning focal lengths. PBS proton beams dispose on the other hand of an unmatched technology readiness level as a candidate modality for treating deep-seated tumours with FLASH-RT [5,7,8,23–28]. They provide a clinically used and proven RT treatment technology and existing clinical proton treatment units, which can be modified and upgraded to achieve UHDR. Advances in accelerator technologies and patient positioning may decrease cost and size footprints of future proton therapy and VHEE therapy units [61]. This may make cost and size differences between the modalities less pertinent. Other promising alternative FLASH-RT delivery techniques than scanned VHEE and TP have been proposed for treating deep-seated tumours. These include UHDR proton treatments using patient-specific 3D range modulators to enable conformal proton UHDR that takes advantage of the Bragg peak and UHDR MV photon linacs [5,8,59].

Apart from dosimetric and technological considerations, there may exist systematic differences in the FLASH effect (and its magnitude) that is produced by TP and VHEE beams, which may result in a clinical incentive to choose one modality over the other. Comprehensive dedicated studies on this subject are still missing. A recent study reported a similar reduction in radiation damage for both 30 MeV electron beams and 224 MeV proton beams for zebra fish embryos irradiated with either conventional dose rate (CONV) or UHDR [62]. Another recent study reports similar sparing of mice brain function and similar tumour control for 150 MeV protons and 5.5 MeV electrons [63]. Similar magnitudes of UHDR sparing have also been observed for electrons (~10 MeV) and protons in mice skin [2]. In summary, findings so far are consistent with the assumption that similar magnitudes of the FLASH effect can be achieved by both electron and proton treatments, but dedicated studies comparing VHEE and TP beams are needed.

Conclusion

This study demonstrates little to no dosimetric incentives for TP-based FLASH-RT treatments when compared with VHEE-based FLASH-RT for VHEE beams of sufficient energy (≳150 MeV), and indicates that for some cases VHEE-based FLASH-RT with energies as low as 100 MeV may provide acceptable dosimetric plan quality compared to TP-based FLASH-RT. Dedicated comparative studies are needed to assess potential biological differences between TP and VHEE delivery modalities in more detail.

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: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jean-François Germond:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Laurent Desorgher:** Resources, Software, Validation, Writing – review & editing. **Izabella Veres:** Resources, Validation, Writing – review & editing. **Andreas Bratel:** Resources, Software, Visualization, Writing – review & editing. **Eric Landström:** Resources, Software, Visualization, Writing – review & editing. **Erik Engwall:** Resources, Software, Visualization, Writing – review & editing. **Fernanda G. Herrera:** Supervision, Validation, Writing – review & editing. **Esat Mahmut Ozsahin:** Supervision, Validation, Writing – review & editing. **Jean Bourhis:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing. **François Bochud:** Conceptualization, Funding acquisition, Project administration, Supervision, Validation, Writing – review & editing. **Raphaël Moeckli:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

Andreas Bratel, Eric Landström and Erik Engwall are employees of RaySearch Laboratories AB. The other 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.2024.110177.

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