TITLE: Assessment of the quality of very high-energy electron radiotherapy planning.

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36 **Abstract**

Background and Purpose: To assess the quality of very-high energy electron (VHEE) scanning pencil beam radiation therapy in relation to state-of-the-art volumetric modulated arc therapy (VMAT) and to determine the extent of its application.

40 **Material and Methods:** We planned five clinical cases with VHEE scanning pencil beams of 100 and 120 MeV, equally distributed in a coplanar arrangement around the patient. The clinical cases included acoustic neuroma, and liver, lung, esophagus, and anal cancer cases. We performed Monte Carlo (MC) dose calculations and we optimized the dose in a research version
44 of RayStation. VHEE plan performance was compared against clinically delivered VMAT.

Results: With equal target coverage, mean doses to organs at risk (OARs) were on average 22% lower for the VHEE plans compared to the VMAT plans. Dose conformity was equal or superior compared to the VMAT plans and integral dose to the body was in average 14% (9%-22%)
48 lower for the VHEE plans.

Conclusions: The dosimetric advantages of VHEE as demonstrated for a variety of clinical cases, combined with the theoretical ultra fast treatment delivery, afford VHEE scanning pencil beam radiotherapy a suitable and potentially superior alternative for cancer radiotherapy.

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Introduction

The use of electron beams in radiation therapy has been limited to the treatment of superficial lesions due to electrons short range at the clinically available energies. Previous studies have shown the potential advantages of using very high energy electrons (VHEE) of 100 MeV to 250 MeV for the treatment of deep-seated lesions [1–4]. VHEE beams are characterized by a penetrating ability comparable to clinical photon beams in tissue (>40 cm for 150 MeV [1]), reduced scattering in air and tissue, and absence of electronic disequilibrium at interfaces with varying densities which favors a more uniform dose distribution throughout the target [1,2]. These VHEE physical characteristics contribute to enhance the ratio of target dose to dose to healthy tissue [4–6]. Additionally, VHEE radiation therapy could be delivered using pencil beam electromagnetic scanning techniques, eliminating with this the dependence on moving mechanical devices, opening the possibility of a very fast irradiation.

These ideas led our group to propose a conceptual design of a compact treatment machine able to deliver VHEE scanning pencil beams from multiple angles using fixed beam lines equally-spaced in a coplanar arrangement around the patient [7]. Pencil beams of adjustable sizes, would be rapidly raster-scanned over an area covering the beam's-eye-view of the target to produce intensity-modulated fields from each beam's direction. A high-efficiency and high-gradient LINAC design [8] would be required for the system to fit in existing radiation therapy vaults. Before facing the technical challenges of building a VHEE machine it would be necessary to determine: 1) the cases that may be treated with VHEE radiation therapy and 2) the combination of beam parameters that could lead to a successful treatment planning and that would become the input for the design of our VHEE treatment machine.

76 In a previous work [5] we presented the workflow for radiotherapy with very high-energy
electron beams and demonstrated the superiority of VHEE dose distribution for a pediatric brain
case and a lung case as well as its equivalence for a prostate case compared to volumetric
modulated arc therapy (VMAT). The present study aimed to extend the application of VHEE
80 treatment planning to a larger number of anatomic sites considering a realistic pencil beam
emittance [9]. In this work we presented VHEE dose distributions for five clinical cases
calculated by means of Monte Carlo simulations. We also included a comparison between VHEE
and the clinically delivered VMAT dose distributions to state the quality of VHEE plans
84 compared to the current state-of-the-art photon radiation therapy technique.

Materials and methods

88 We selected five clinical cases to be planned for radiotherapy with VHEE pencil beam scanning.
VHEE pencil beams of energies 100 and 120 MeV and sizes of 0.1-0.5 cm full width at half
maximum (FWHM) were calculated using BEAMnrc/EGSnrc [10,11] MC code. Phase space
data (PSD) was generated considering a monoenergetic elliptical beam with Gaussian
92 distribution and an emittance of 0.3° (half-angle). The beam emittance was set based on the
characteristics of the high energy electron beam from the Next Linear Collider Test Accelerator
(NLCTA) located at the SLAC National Accelerator Laboratory [9].

We considered an array of multiple fixed coplanar beam lines (16 or 32) equally spaced around
96 the patient with a 50 cm distance from the end of the electron beam line to the isocenter. The
spacing between pencil beams could also be modified (from 0.1 cm to 0.5 cm at isocenter).

VHEE treatment planning

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We ran DOSXYZnrc/EGSnrc [12] MC simulations for pencil beam dose calculation, of each beam of the treatment plan, using a Matlab (The Mathworks, Nattick, MA) graphical user interface (GUI) developed by our group [5]. MC-simulated pencil beam dose data corresponding to the whole treatment plan were imported into RayStation (RaySearch Laboratories AB, Stockholm Sweden) for spot-scanning inverse treatment planning. Optimization was done using a modified version of RayStation's proton pencil beam scanning optimization algorithm [5].

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The objectives and constraints used for the optimization were set based on the dose volume histogram (DVH) of the corresponding VMAT plan. VHEE and VMAT plans were normalized so 95% of the PTV was covered by 100% of the prescription dose, which is how the clinically delivered VMAT plans were prescribed.

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We calculated DVHs, mean dose to the organs at risk (OARs) and conformity indices CI_{100} and CI_{50} . Conformity index CI_x was defined as the ratio between the volume covered by x% of the prescription dose and the planning target volume (PTV).

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Clinical cases

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The studied clinical cases were: acoustic neuroma, and liver, lung, esophagus and anal cancer cases. Target sizes ranged from 1 cm^3 to 990 cm^3 (Supplementary Table 1).

Four of the cases were treated using coplanar VMAT. Only the acoustic neuroma case was treated with non-coplanar 6MV photon beams from a CyberKnife (CK) robotic stereotactic radiosurgery system (Accuray, Sunnyvale, CA) [13].

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Several VHEE plans, with different energy (100 and 120MeV), pencil beam size/spacing (0.1-0.5 cm/0.1-0.5 cm) and number of equidistant coplanar beams (16 or 32) were generated for each clinical case. We then compared the VHEE plans with each other and selected the one that provided the highest dose sparing to OARs and the highest dose conformity to compare it with the clinically delivered VMAT plan. In this work we present only the best VHEE plan for each clinical case.

Results

Anal cancer case

The anal case had two PTV structures with prescription doses of 40 Gy and 45 Gy. A comparison between the dose distributions of the VHEE plan and the 15 MV VMAT plan (3 arcs) is shown in Figure 1.

VHEE plan consisted of 32 100 MeV beams and a pencil beam size/spacing of 0.5 cm/0.5 cm. The VHEE plan provided the same target coverage as the VMAT plan to both PTV structures. Furthermore, the VHEE plan was more conformal than the VMAT plan in all selected planes: axial, coronal and sagittal (Figure 1-a). This was confirmed by indices CI_{100} and CI_{50} . The $CI_{50}=4.94$ of the VHEE plan was lower than the $CI_{50}=6.69$ of VMAT. CI_{100} indices were similar for the two plans (Supplementary Table 1).

The DVH comparison (Figure 1-b) demonstrated the superior normal tissue dose sparing provided by the VHEE plan. In general, the VHEE plan reduced the mean doses to most of the OARs (Figure 1-c), including a reduction of 21.8% and 18.5% to the genitalia and perineum,

respectively. Also, the integral dose (mean dose to the body structure) was reduced by 13% when planning with VHEE pencil beams.

148 Esophagus cancer case

This case also had two PTV structures, with prescription doses of 45 Gy and 50 Gy. Figure 2 shows the comparison between the 6MV VMAT plan (3 arcs) and the corresponding VHEE plan.

152 The VHEE plan was composed of 32 120 MeV beams with pencil beam size/spacing of 0.5 cm/0.5 cm.

The VHEE plan was more conformal than the VMAT plan for the two PTV structures as can be seen from the dose distributions in Figure 2-a. Conformity indices $CI_{100}=1.05$ and $CI_{50}=3.18$ of the VHEE plan were lower than the $CI_{100}=1.09$ and $CI_{50}=4.78$ of the VMAT plan. DVHs showed a general OARs dose reduction when using VHEE (Figure 2-b) especially for doses lower than 35 Gy (~76% of the prescription dose). OARs mean doses were systematically lower for the VHEE plan (Figure 2-c) with a 23% and 20% lower mean dose to the spinal cord and heart, respectively. The integral dose was also reduced by a 22% when using VHEE pencil beams.

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Acoustic neuroma case

164 The PTV in this case had a volume of only 1 cm^3 and was located at a maximum depth of 12 cm in the AP direction. The VHEE plan was composed of 32 120 MeV beams and pencil beam size/spacing of 0.1 cm/0.1 cm. A comparison between the VHEE treatment plan and the clinically delivered CyberKnife plan (84 beams) is presented in Figure 3.

168 In order to make a fair comparison amongst coplanar plans, an additional 6 MV VMAT plan (2
arcs) was calculated. The comparison between dose distributions (Figure 3-a) showed the high
conformity of the CK plan, followed by the VHEE and the VMAT plan, in that order, as
confirmed by their conformity indices. $CI_{100}=1.22$ and $CI_{50}=8.91$ of VHEE treatment plan were
172 higher than the $CI_{100}=1.06$ and $CI_{50}=5.59$ of the CK plan but lower than the $CI_{100}=1.36$ and
 $CI_{50}=9.23$ of the VMAT plan. The same PTV coverage was achieved by the three plans (Figure
3-b). The most relevant difference between the plans regarding OARs dose sparing was for the
right cochlea. The VHEE plan provided 12% lower mean dose to the right cochlea than CK but
176 15% higher mean dose than the VMAT plan. Integral dose was not significantly different
between the plans.

Lung cancer case

180 The comparison between the 10 MV VMAT plan (1 arc) and the corresponding VHEE plan
showed the same PTV coverage and dose homogeneity for both plans (Supplementary Figure
S1). The VHEE plan consisted of 16 100 MeV beams. The pencil beam size/spacing was
184 reduced accordingly to the target size (Supplementary Table 1) to 0.3 cm/0.3 cm.

The difference between the plan's DVHs was more subtle than for the previous clinical cases.
However, the mean doses for all the OARs were still lower for the VHEE plan (Supplementary
Figure S1) with the bronchial tree receiving 21% lower dose. Integral dose in this case was
188 reduced by a 10% when using VHEE pencil beams. This modest reduction in integral dose was
also reflected in the 13% difference between the conformity indices $CI_{50}=2.98$ for the VHEE

plan and 3.42 for the VMAT plan. $CI_{100}=0.95$ of the VHEE was lower than the $CI_{100}=0.97$ of the VMAT, fulfilling accurately the prescription dose.

Liver cancer case

The target volume in this case was the second smallest of the five cases presented in this work (9 cm³) and it was the most superficially located ~ 6 cm in depth (Supplementary Figure S2). The VHEE plan consisted of 32 120 MeV beams and pencil beam size/spacing of 0.3 cm/0.3 cm. A comparison between the VHEE plan and the 10 MV VMAT plan (1 arc) is presented in Figure 4. The VHEE plan was more heterogeneous than the VMAT plan, as shown by the DVH comparison included in the supplementary material (Supplementary Figure S2). Maximum dose to the PTV, defined as the dose to 2% of the volume, was 115% and 127% of the prescribed dose for the VMAT and VHEE plans, respectively. However, in this case, due to the reduced size of the PTV, a higher dose > 120% of the prescription dose to the target volume was desirable, and as shown by the dose distributions and DVH, achievable when using VHEE pencil beams. The PTV dose increase was not accompanied by a scale in dose to the OARs. OARs mean doses were very similar between the plans (Supplementary Figure S2). The most relevant difference between the plans was a 19% lower dose to the chest wall for the VHEE plan. Conformity indices CI_{100} (0.99 for VMAT and 0.98 for VHEE) and CI_{50} (4.36 for VMAT and 3.25 for VHEE) showed the higher conformity of the VHEE plan. However, integral dose was not significantly different between the plans.

A summary of the conformity indices CI_{100} and CI_{50} for all the cases and treatment plans is listed in Table 1. (Supplementary Table 1).

Discussion

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In a previous work we demonstrated that 100 MeV VHEE dose distributions for a pediatric brain case and a lung case outperformed the VMAT plans while a 100 MeV prostate dose distribution was similar to the clinical VMAT plan [5]. This work investigated the application of VHEE pencil beams to five additional anatomical sites considering a realistic pencil beam emittance of 0.3° . In order to assess the quality of VHEE treatment planning and determine the extent of its application we compared the VHEE plans to the corresponding clinically delivered VMAT plans. In all the cases, VHEE provided more conformal dose distributions and target coverage of comparable quality than that offered by VMAT. This is a consequence of the penetrating ability of very high energy electrons (>40 cm for 150 MeV) and the use of multiple equidistant beams around the patient, which maximizes the dose to the target while reducing the dose to normal tissues. The cases that benefited most of these characteristics were the ones with targets > 4 cm that were more centrally located like the anal, esophagus, and lung cases presented in this work, in agreement with literature [1]. We demonstrated that VHEE dose distributions provide a higher normal tissue dose sparing than the corresponding VMAT plan. While in the cases with smaller sized, shallower targets (acoustic neuroma and liver cancer) the VHEE dose distributions provided a similar normal tissue sparing than the VMAT plan and a more heterogeneous dose distribution inside the PTV (higher dose), which can be desirable in the case of small targets. Based on the evaluated cases, from this and the previously published work [5], the possible parameters for the design of the VHEE treatment machine could be: 32 beams equally spaced

around the patient of 100 MeV pencil beams and a scanning resolution of 0.3 cm (pencil beam size/spacing).

The reduction of mean dose to OARs and the lower integral dose provided by the VHEE plans compared to the clinically delivered VMAT plans, together with the possibility of a very fast treatment delivery (of the order of ~ 117 Gy/s [5]) support the idea of using VHEE scanning pencil beams as an alternative radiation therapy technique. Furthermore, the use of such high dose rate could represent a radiobiological advantage, as a recent in-vivo study has shown that the use of a high dose rate ≥ 40 Gy/s can reduce the occurrence and severity of early and late complications affecting normal tissue while obtaining the same tumor control [14].

In this work we demonstrated that the use of 100 to 120 MeV very high-energy electron scanning beams for radiation therapy can be extended to other anatomic sites such as anal, esophagus, lung and liver cancer and acoustic neuroma.

We observed that, similar or superior dose distribution can be achieved by VHEE scanning pencil beam radiation therapy compared to the VMAT, even when a more realistic pencil beam emittance is considered. We confirmed that these advantages are consistent for a wide range of target volumes with an enhanced normal tissue sparing when the targets are more centrally located inside the patient (depths > 10 cm). These results, together with our previously published work [5], encouraged the design of a VHEE treatment machine [7]. The design of the VHEE treatment machine is still under investigation. In the future a design of non-coplanar VHEE beams distributed around the patient will be explored in an attempt to further improve VHEE dose distributions. In conclusion, VHEE scanning beam radiation therapy, due to its dosimetric advantages and fast treatment delivery, has the potential to become an alternative cancer treatment modality worth of being further investigated.

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Figure Legends

Figure 1. Anal case dose distributions (a), DVHs (VHEE in solid line and VMAT in dashed line) (b), and organ mean doses (c) for the VHEE plan and the clinically delivered 15MV VMAT plan.

Figure 2. Esophagus case dose distributions (a), DVHs (VHEE in solid line and VMAT in dashed line) (b) and organ mean doses (c) for the VHEE plan and the clinically delivered 6MV VMAT plan.

Figure 3. Acoustic case dose distributions (a), DVHs (b) and organ mean doses (c) for VHEE, 6MV VMAT and the clinically delivered CK plan.

Figure1

Figure 3

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