Clinical microbeam radiation therapy with a compact source: specifications of the line-focus X-ray tube

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ABSTRACT

Background and purpose: Microbeam radiotherapy (MRT) is a preclinical concept in radiation oncology with arrays of alternating micrometer-wide high-dose peaks and low-dose valleys. Experiments demonstrated a superior normal tissue sparing at similar tumor control rates with MRT compared to conventional radiotherapy. Possible clinical applications are currently limited to large third-generation synchrotrons. Here, we investigated the line-focus X-ray tube as an alternative microbeam source.

Materials and methods: We developed a concept for a high-voltage supply and an electron source. In Monte Carlo simulations, we assessed the influence of X-ray spectrum, focal spot size, electron incidence angle, and photon emission angle on the microbeam dose distribution. We further assessed the dose distribution of microbeam arc therapy and suggested to interpret this complex dose distribution by equivalent uniform dose.

Results: An adapted modular multi-level converter can supply high-voltage powers in the megawatt range for a few seconds. The electron source with a thermionic cathode and a quadrupole can generate an eccentric, high-power electron beam of several 100 keV energy. Highest dose rates and peak-to-valley dose ratios (PVDRs) were achieved for an electron beam impinging perpendicular onto the target surface and a focal spot smaller than the microbeam cross-section. The line-focus X-ray tube simulations demonstrated PVDRs above 20.

Conclusion: The line-focus X-ray tube is a suitable compact source for clinical MRT. We demonstrated its technical feasibility based on state-of-the-art high-voltage and electron-beam technology. Microbeam arc therapy is an effective concept to increase the target-to-entrance dose ratio of orthovoltage microbeams.

1. Introduction

Certain inoperable tumors such as glioblastoma multiforme remain to have poor prognosis, despite advances in modern cancer care. The effectiveness of radiotherapy is limited by radiosensitive organs at risk close to the tumor. The yet preclinical concept of microbeam radiation therapy (MRT) [1] has shown superior normal tissue sparing at similar tumor control rates compared to conventional radiotherapy [2,3] and is therefore promising for treating aggressive tumors. MRT utilizes spatial fractionation [4] of the dose distribution into an array of quasi-parallel, planar photon beams of 25–100 μm width and unconventionally high doses of hundreds of Grays at the target. These high-dose regions (peaks), separated by 100–400 μm, alternate with low-dose areas (valleys). The biological effects of MRT are not fully understood yet [5], and it is still unclear if a spatially fractionated target dose is more efficient than a homogeneous target dose [2]. Nevertheless, authors agree that a low valley dose, a high peak-to-valley dose ratio (PVDR), and steep lateral penumbras from the peaks to the valleys are crucial for sparing healthy tissue [5–7].

Mean photon energies of 100–150 keV give the best compromise

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between short ranges of secondary electrons, allowing steep lateral penumbras, and shallow depth doses for reaching deep-seated tumors [7–10]. The radiation source needs low divergence and a focal spot smaller than an individual microbeam to maintain the dose pattern and sharp beam penumbras in larger depth in the tissue [11]. A high dose rate, up to kilorads per second, prevents blurring of the microbeam pattern caused by organ motion [7].

These requirements are fulfilled at some third-generation synchrotrons [7]. However, the limited availability, enormous size, and high costs render synchrotrons unfeasible for routine clinical radiotherapy.

For a clinical MRT, compact sources are required. Various concepts have been suggested, including inverse Compton scattering sources [12], carbon nanotube field emission technology [13], and conventional X-ray tube-based sources [14,15]. However, none of the suggested alternatives to synchrotrons achieve dose rates adequate to patient treatments. A strategy that might succeed in sufficiently high dose rates is the line-focus X-ray tube [11].

In this study, we investigated the technical feasibility of the line-focus X-ray tube for clinical application in MRT. State-of-the-art electron accelerators [16,17] provide beam currents of 1 A at 500 keV energy and therefore generate sufficient electron beam power. However, it is challenging to focus beams to a micrometer-sized focal spot. Moreover, such an accelerator requires high-voltage (HV) pulses in the megawatt range for several seconds, which commercially available HV generators struggle to deliver. We investigated the suitability of modular multi-level converters (MMCs) from the high-voltage direct-current transmission technology. Finally, we analyzed the dose distribution of the line-focus X-ray tube and showed that microbeam arc therapy can be a strategy to avoid high beam entrance doses of orthovoltage x-rays.

2. Materials and methods

The line-focus X-ray tube is a modified X-ray tube with two unique features: a strongly eccentric focal spot with a width of tens of micrometers and a high target surface velocity of 200 m s−1. These two features shift the physical characteristics of target heating from the heat conduction limit for conventional X-ray tubes to the heat capacity limit [11]. In the heat capacity limit, the current density can be increased while keeping the focal spot temperature below the target melting point. With these high electron currents, X-ray dose rates of a few hundred Grays per second can be achieved to avoid blurring of the dose pattern due to organ motion. A multislit collimator shapes the uniform radiation field into microbeams. For a clinical application, the line-focus X-ray tube is required to deliver a dose rate of above 100 Gy/s (50 cm from the focal spot) with an acceleration voltage of 600 kV, a power of 1.5 MW, an electron current of 2.5 A, and a focal spot size of 0.05 × 20 mm2 [11].

The next subsections build up on these quantities and provide a possible realization of the components and applications. We developed an HV supply, considering its power consumption, energy storage and insulation, and an electron source which meets the demand of a small emittance from the cathode through the quadrupole to the target. The microbeam field was optimized regarding the X-ray spectrum, focal spot size, electron incidence angle, and photon emission angle. Microbeam arc therapy was investigated with a head phantom study.

2.1. High-voltage supply

Due to the low overall efficiency of X-ray tubes in the single-digit percentage range, high dose rates lead to a particularly high power consumption. The HV supply for the line-focus X-ray tube was to be designed for an output power of 2 MW, an output voltage of 600 kV (±300 kV referred to earth potential), and irradiation times of 5 s with an interval of 1200 s [11]. A commercially available HV supply does not exist for these requirements. Main design challenges of a new supply concept were reduced to the following points:

The high output voltage of the converter affects the usable HV semiconductors, the converter topology and the insulation concept. Modern power semiconductors have a maximum blocking voltage of 6.5 kV so that the system supply cannot be implemented monolithically.

The energy supplier requires a continuous input power since peak loads of 2 MW lead to considerable disturbances in the public grid. The continuous input power requires a buffering, which is typically achieved by batteries. Considering the irradiation intervals, the average power consumption is reduced to approximately 10 kW.

Adjustment options for the voltage amplitude as well as the voltage slope of the converter are necessary as even small parasitic components such as earth capacitance lead to high unintended interferences during the switching event for these high voltages.

A distributed energy storage is beneficial as smaller units are easier to handle in case of malfunction. Using a single rechargeable battery would require considerable constructive and structural precaution.

The design challenges are comparable to those in modern high-voltage direct-current transmission, where they are met by modular multi-level converters (MMC) [18]. An MMC is based on identical units as individually switchable voltage sources. A series connection of these voltage sources can generate high output voltages with low blocking voltage components. For the line-focus X-ray tube, we developed an HV supply concept based on an adapted MMC.

2.2. Electron beam

The HV supply provides the power for the electron source which accelerates and focuses the beam onto the target. The generation of a micrometer-sized focal spot requires high electron beam quality. For the line-focus X-ray tube, in particular the emittance ε, a conserved quantity characterizing beam size z and divergence z′ = dz/dx, has to be small. The normalized root mean square (rms) emittance is defined as

$$\epsilon_{\text{rms}} = \gamma \beta \sigma_z \sigma_z' - \left( \sigma_z' \right)^2.$$  \hspace{1cm} (1)

The dimensionless parameters γ and β are the Lorentz factor and the velocity divided by the speed of light, respectively. (σ2) represents the second moment of the z-distribution. Space-charge fields arising from high beam currents and relatively low kinetic energies needed to be incorporated into the electron source development as they defocus the beam and lead to unwanted growth.

At the end of the beamline, a quadrupole magnet can form an eccentric beam spot by focusing in one dimension and defocusing in the other. An advantage of the quadrupole is the possibility to vary the spot size.

A first approach to calculate the demanded emittances and beam dimensions upstream of the quadrupole were the K-V-equations [19] which describe space-charge effects on the beam size. In front of the proposed quadrupole, the beam diameter needed to be smaller than 10 mm to avoid the stray field on the periphery of the quadrupole which causes emittance growth. This led to a maximum emittance of 0.2 mm assuming a focal width of 50 μm. In addition, spherical aberration limits the focal size.

To extract the required currents with a long lifetime and low emittance, thermionic cathodes are the best choice. The normalized rms emittance of a thermionic cathode is given by

$$\epsilon_{\text{rms}} = \frac{d_{\text{cath}}}{4} \left( \frac{k_B T}{m_e c^2} \right),$$  \hspace{1cm} (2)

where d_{cath} is the cathode diameter in the direction of interest, k_B T the thermal energy, and m_e c^2 the electron rest mass energy [20]. A small cathode needs to have high temperature for high output currents. The maximum temperature of a barium tungsten dispenser cathode (Type: 411 M) recommended by the manufacturer is 1190°C, which results in a
current density of 15 A cm\(^{-2}\) [21]. For a current of 2.5 A and a circular emission area, the theoretical cathode emittance is thus 0.6 mm.

Optionally, a rectangular cathode can be used with the advantage of a smaller beam size and therefore a sufficiently small emittance in one direction. Nevertheless, a quadrupole is necessary for focus adjustment.

Tracking simulations with CST [22] were performed to find an appropriate design for the electron source. At the electrode structure, electric fields above 10 MV m\(^{-1}\) had to be avoided to reduce the risk of electrical breakdown.

2.3. X-ray optimization

At the focal spot, the accelerated electrons hit the target and create a divergent X-ray field which is shaped into microbeams by a multislit collimator. The radiation transport of the line-focus X-ray tube was simulated with Monte Carlo in Geant4 (version 10.4.2, Penelope physics library). A parallel electron beam (200–800 keV) hit the cylindrical tungsten target on the front face in an eccentric Gaussian-shaped focal spot. The spot width was varied between 10 and 500 μm, the spot length between 5 and 40 mm.

The generated x-rays traveled through a 0.8 mm beryllium window, aluminum or copper filters of different thickness, and a microbeam collimator (field size 20 × 20 mm\(^2\), divergent slits of 50 μm × 20 mm [23,24]), which was positioned 50 cm from the focal spot. The absorber thickness of the collimator was adjusted to the maximum photon energy for less than 0.25% leakage radiation. This resulted in a total tungsten thickness of 7–35 mm depending on the initial electron energy. Attached to the collimator, a water phantom served as detector with a thickness of 40 mm. The generated x-rays traveled through a 0.8 mm beryllium window, aluminum or copper filters of different thickness, and a microbeam collimator (field size 20 × 20 mm\(^2\), divergent slits of 50 μm × 20 mm [23,24]), which was positioned 50 cm from the focal spot. The absorber thickness of the collimator was adjusted to the maximum photon energy for less than 0.25% leakage radiation. This resulted in a total tungsten thickness of 7–35 mm depending on the initial electron energy. Attached to the collimator, a water phantom served as detector with a thickness of 40 mm.

The investigation of the microbeam dose distribution was separated into the influence of the X-ray spectra, the focal spot size, and the electron incidence angle onto the target as well as the X-ray emission angle. The angles were optimized for maximum energy deposit in water, corresponding to maximum dose rate. At the end, PVDR values achievable with optimal X-ray field parameters are presented.

As a PVDR comparison to state-of-the-art MRT with parallel beams, Geant4 simulations were carried out with parallel X-ray microbeams and the spectrum from the ID17 biomedical beamline at the European Synchrotron Radiation Facility in Grenoble, France. The spectrum at ID17 has a maximum energy of 250 keV and a mean energy of 104 keV [25].

3. Results

3.1. High-voltage supply

The developed concept of the energy supply in Fig. 1 represents an adapted version of a conventional MMC where the capacitor was replaced by a DC/DC converter. The DC/DC converter boosts the battery voltage into the kilovolt range. The complementary power switches \((S_1\) and \(S_2\)) bridge or insert the sub-module in the module chain: As soon as \(S_1\) is opened, \(S_2\) is closed and the output terminals are short-circuited so that no voltage is added to the main output voltage. In the other case, \(S_1\) is closed and the sub-module voltage \(V_k\) is added to the voltage sum of the converter \(V_{DC}\):

\[
V_{DC} = \sum_{k=1}^{k} V_k = \sum_{k=1}^{k} n\cdot V_{bus_k}
\]

(3)

This approach allows to accurately set the level and slope of the output voltage even during operation.

To avoid manual handling during the charging process, the batteries are charged through the main DC-link terminals: All modules are bypassed beside the one to be charged. By an automated switching through all modules, a single low-voltage power supply can charge the batteries. A slight adaption of the sub-module DC/DC converter is

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**Fig. 1.** Modular DC/DC converter setup with distributed energy storage.
necessary to enable a bidirectional power flow.

As seen in Fig. 2, the design of the sub-modules is based on a planar transformer with its windings integrated into the printed circuit board (PCB). To reduce the insulation distances, the cooler is referenced to the negative pole of the battery voltage and to half the output voltage. Thus no voltage of the module exceeds 1 kV in relation to the cooler. The specifications of each of the 300 sub-modules are the following: 6.67 kW output power, 2 kV output voltage, 3.33 A output current, and 12-3.7 V battery voltage.

The presented HV setup can safely supply the electron source with sufficient power to generate high electron beam currents and thus high X-ray dose rates of above 100 Gy/s.

3.2. Electron beam

The result of the electron source setup optimized with CST is shown in Fig. 3. To suppress emittance growth due to space-charge fields of the electron beam, a high gradient of the accelerating electric field was mandatory. This high gradient was achieved by a small distance between cathode and anode. A Pierce electrode focused the electron beam to a size small enough to avoid the stray field of the quadrupole. An acceleration tube further accelerated and focuses the beam by several electrodes with increasing electric potential. Behind the acceleration tube, a quadrupole magnet formed an eccentric beam spot. The simulations showed that the achievable emittance was smaller with a rectangular than with a circular cathode.

3.3. X-ray optimization

3.3.1. Influence of the X-ray spectra

For highest PVDR and steepest penumbras, the electron energy should be 300–400 keV, as seen in Fig. 4a. In simulations, beams of lower energy had a steeper depth-dose curve and a lower PVDR in depth. With higher energies, secondary electrons scattered from the peak farther into the valley region which increased the valley dose, decreased the PVDR, and increased the penumbra full width at half maximum (FWHM).

For 300 and 400 keV electrons, a filter of 0.4 mm copper (resulting in 97 and 109 keV mean photon energy, respectively) was a good compromise between high PVDR, steep penumbras, shallow depth dose, and high relative output.

3.3.2. Influence of the focal spot size

The Gaussian standard deviations of the focal spot should not be larger than an individual collimator slit, resulting in a maximum spot size of 50 μm x 20 mm for the used collimator. A spot wider than 50 μm resulted in a lower PVDR (see Fig. 4b) and broader penumbra and FWHM. A further reduction in spot width had no impact on the microbeam dose distribution or PVDR, which can be seen from the comparison to a point source in Fig. 4b. Longer spots only increased the longitudinal penumbras.

3.3.3. Influence of the incidence and emission angles

The photon energy deposit was maximum for small electron incidence angles onto the target and exhibited a shoulder region for small photon emission angles (polar angle θ), see Fig. 5. Regarding the azimuthal angle ϕ, the photons were emitted uniformly. Taken an incidence angle of 0° or 10°, emission angles between 0° and 50° resulted in a decrease of less than 5% of the maximum efficiency.

3.3.4. Achievable PVDR values

With the requirements described in 3.3.1 to 3.3.3, a PVDR above 30 was achieved in 10 mm (above 20 in 40–100 mm) water depth for single-field MRT (see Fig. 4a and 4b). The PVDR decreased with depth up to 50 mm due to increased Compton scattering into the valleys. Beyond 50 mm, the PVDR remained constant as peak and valley dose decreased at the same rate. At the rear end of the phantom, the PVDR increased due to less backscattering.

The simulations with parallel microbeams with the ID17 spectrum led to a PVDR of 35 in 10 mm (25 in 40–100 mm) water depth.

3.4. Microbeam arc therapy

With microbeam arc therapy, the peak entrance dose to the cranial bone and to normal brain tissue was considerably decreased and spread over the whole head phantom in x- and y-direction (see Figs. 6a and 6b). Thereby, the tumor peak dose in the center of the phantom decreased by less than 1%.

The central tumor region (x = 70 mm) exhibited a clear peak-valley dose profile as known from single-field MRT as seen in Fig. 6c. The region of highest dose on the periphery of the field (x = 60 mm) was considerably smaller and spread out in z already at few millimeters off the central axis due to field divergence.

Normalized to 2 Gy valley dose, a lower electron energy led to higher dose in the peak regions (see Fig. 6d). In the target center, the PVDR was the same as for single-field MRT in 80 mm water depth: 12, 16, and 12 for 400 keV, 600 keV, and 800 keV, respectively. The peak entrance dose decreased with higher electron energy due to shallower depth-dose curves. For the single field, the target-to-entrance peak dose ratios were 0.059, 0.074, and 0.083; for the rotated field, they were 2.2, 2.8, and 3.1 for 400, 600, and 800 keV electrons, respectively. The gain in target-to-entrance dose ratio by the use of rotation was 37–38, independent of energy.

Fig. 6e shows the EUD distribution for the head phantom with 1 mm³ voxel size. The EUD approximately followed the valley dose with an offset (see Fig. 6f).

4. Discussion

Essential requirements for microbeam treatments are a sufficiently high dose rate and an adequate PVDR. In order to use the line-focus X-ray tube for MRT, we developed concepts for an HV supply and an electron source. For a high PVDR, the eccentric focal spot must be smaller than the microbeam cross section. Microbeam arc therapy can increase the target-to-entrance dose ratio of orthovoltage x-rays, while keeping the PVDR in the phantom center similar to single-field MRT. Microbeam arc therapy can be interpreted by EUD.

The presented modular HV supply fulfills the requirements for high dose rates. Due to the redundancy by many modules, the setup represents a reliable [33] and universal voltage source also for other pulsed applications such as computed tomography or electron cyclotron resonance heating. For high dose rates, the angle-dependent X-ray output power from the target is essential. The electron beam incidence angle should therefore be roughly perpendicular (0–10°).

Regarding the focal spot size, especially its width is critical for successful MRT [11]. Analytical calculations of the electron beam showed the possibility of achieving the required spot size. In simulations, the geometry of the cathode, the Pierce electrode, the anode, and the quadrupole magnet must be optimized. Additionally, we will consider an increased acceleration gradient and cathode types other than barium tungsten disperser cathodes, e.g., lanthanum hexaboride cathodes which have a higher electron yield per area and thus a smaller emitting area. Despite the higher operation temperature of approximately 1800°C, this promises achieving a smaller emittance. Changes in position or size of the focal spot, that may result from intensity fluctuations of the thermionic cathode or from target vibrations, must be kept to a minimum.

For the line-focus X-ray tube, we simulated PVDR values

1 The phantom center was in 80 mm water-equivalent depth considering the relative density of 1.7 for cortical bone.
comparable to those measured with same field size of $20 \times 20 \text{ mm}^2$ at the ID17 [34] where MRT experiments have been successfully performed [2,35,36]. The simulations with parallel microbeams for the line-focus X-ray tube led to PVDR values that were 20% higher in 40–100 mm water depth, which was reasonable considering the missing field divergence. The PVDR trend over depth (as in Fig. 4a and 4b) has been observed before for parallel microbeams [34]. We confirmed an optimal mean photon energy of approximately 100 keV [8,9]. However for clinical treatments of e.g. brain tumors, higher mean energies might be required [7]. A higher energy leads to deeper penetration and a higher target-to-entrance dose ratio which better spares healthy tissue at the same tumor dose.

For further healthy tissue sparing, microbeam arc therapy, similar to conventional arc therapy, is useful for clinical MRT. With the same
objective of lower peak entrance doses, microbeam multi-port irradiations with a limited number of incidence angles [13,37–40] and a spiralMRT [41] have been suggested. In contrast to most published concepts, our method entails a spatially fractionated dose not only to beam entrance regions but also to the tumor which might further widen the therapeutic window [2].

Microbeam arc therapy generated complex dose distributions with intersecting peaks of varying dose. Currently it is impossible to predict the biological or clinical effect of such beam geometries. The EUD concept was used as an approach to translate the dose distribution of microbeam arc therapy into conventional radiotherapy dose. As the EUD followed the trend of the valley dose, it confirms the observation that normal tissue toxicity depends primarily on the valley dose [2,5,6].

Another medical application of the line-focus X-ray tube might be phase contrast imaging [11]. An additional X-ray exit window at a shallow angle can make the focal spot appear narrower. The very narrow spot together with high dose rates results in a high intensity, spatially coherent beam required for phase contrast imaging [42]. The decrease in dose rate is tolerable for imaging applications.

In conclusion, our simulations demonstrated that the line-focus X-ray tube has great potential as a radiation source for clinical application of MRT. We developed concepts for the high-voltage supply and electron source to deliver high X-ray dose rates from an eccentric electron beam. The compact source can achieve PVDR values comparable to

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Fig. 5. Emission angle-dependent, integrated dose to a water phantom for 300 keV electrons with different electron incidence angles.

Fig. 6a. Dose distribution in the head phantom with microbeam arc therapy (400 kV) with schematic of the microbeam orientation. The dose distribution was symmetric about the z-axis and normalized to 2 Gy valley dose.

Fig. 6b. Dose distribution in the center peak.

Fig. 6c. Field divergence caused a complex dose distribution.

Fig. 6d. Dose profiles at the center of x and y (averaged over 12 mm in x and y).
those of successful preclinical MRT experiments and the presented concepts should be experimentally validated.

Declaration of Competing Interest

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

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