



Applications of Low Energy Megavoltage X-ray Beams in Cancer Radiotherapy

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Authors' contributions

This work was carried out in collaboration between all authors. Author YZ designed the study, searched the literature, and wrote the first draft of the manuscript. Authors YF and JD participated in study design and helped revise the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

A review on the applications of low energy megavoltage (MV) X-ray beams (1-4 MV) in cancer radiotherapy is presented. Firstly, the physical characteristics of low energy megavoltage X-ray beams are reviewed in terms of penumbra, dose fall-off, exit dose, dose to bone, penetration power, skin dose and image quality. Secondly, the therapeutic applications of low energy megavoltage X-rays in cancer radiotherapy are further stratified and discussed based on X-ray energy levels. Thirdly, a systematic review of imaging applications of low energy megavoltage X-ray beams in image-guided radiation therapy (IGRT) and megavoltage fan beam computed tomography (MVFBCCT) is provided. Finally, we summarize the latest development of low energy megavoltage X-ray beams in cancer radiotherapy and cancer imaging during the past twenty years. With their intrinsic physical characteristics, it is feasible to achieve personalized radiotherapy and personalized imaging protocols for individual patient. However, further technological developments and more clinical data would be needed to fully exploit the potentials of low energy megavoltage X-ray beams in the personalized radiotherapeutic management of cancers.

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1. INTRODUCTION

Although 6 MV and higher megavoltage X-ray beams have been dominantly used for decades in clinical radiotherapy, low energy megavoltage X-rays in the range of 1 to 4 MV have started to gain a lot of momentum recently [1,2]. One major reason is that low energy megavoltage X-rays have narrower penumbra due to smaller range of secondary electrons [2], suitable for delivering a compact dose distribution around tumor volume. Another reason is that fast dose fall-off and low exit dose associated with low energy megavoltage X-rays would benefit the critical structures downstream, which is especially favorable for hypofractionated radiation therapy such as stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) where a high dose to the tumor with a highly conformal dose distribution is desired [3].

In addition, it has been demonstrated that real-time imaging and patient positioning can be achieved via the use of modified megavoltage X-ray beams (6 MV) and low-Z material targets (e.g., Al and Cu) in the linear accelerators (Linac) [4]. The benefit of this approach lies in the fact that a single MV X-ray beam can be used for beam's-eye-view imaging and target tracking simultaneously during radiotherapy delivery. With improved image quality from low energy X-rays [5], it would be possible to have a Linac equipped with low energy X-rays (1-4 MV) for radiotherapy and imaging concurrently for enhanced clinical efficiency.

In the following, we will first review the physical characteristics of low energy megavoltage X-ray beams, followed by their clinical applications in radiation therapy as well as imaging. A summary and outlook will be provided in the end.

2. PHYSICAL CHARACTERISTICS OF LOW ENERGY MEGAVOLTAGE X-RAYS

In cancer radiotherapy treatments, it is desirable to deliver a highly conformal and homogeneous target dose while minimizing dose to adjacent critical structures. The popularity of high energy photon beams (≥ 6 MV) in the clinic is largely due to their dosimetric advantages including sufficient penetration power, low skin and bone dose and

very forward-directed photon scattering. However, deep penetration in high energy photons leads to a high exit dose to the critical structures downstream. The build-up and build-down effects between medium boundaries also become more pronounced in high energy photons [6]. The neutron contamination is yet another concern for not only patients but also radiotherapy practitioners [7]. In comparison, low energy megavoltage X-rays (1-4 MV) possess intrinsic physical characteristics which make them beneficial for a variety of radiotherapy practices.

In the following sections, physical characteristics of low energy megavoltage X-rays in terms of penumbra, dose fall-off, dose to bone, penetration power, skin dose and image quality are discussed in detail.

2.1 Penumbra

A diminished penumbral width is fundamental to achieving a steep dose gradient. The penumbra of a treatment beam indicates the rate of dose fall-off laterally, and is usually defined as the lateral distance between 80% and 20% isodose lines at a defined depth (e.g., depth of d_{max} or 10 cm) and field size (e.g., 10 cm x 10 cm) in water [8]. In general, the penumbra degrades dose distribution conformity by spreading dose into adjacent normal tissues. It also degrades dose distribution homogeneity as the edge of treated volume receives less dose [1].

It has been a widely-held belief that increasing photon energy favors forward photon scatter and reduces beam penumbra [1]. This works well for standard radiation field sizes where photon scattering makes a dominant contribution to beam penumbra. However, it is found that for field sizes less than 4 x 4 cm², the secondary electron range is the primary contributor to radiological penumbra [9], which means the radiological penumbra will be reduced as photon energy decreases [10]. With increasing use of intensity-modulated radiotherapy (IMRT) and stereotactic radiosurgery and thereby increasing use of small fields, narrower penumbra would be advantageous for low energy megavoltage X-rays in cancer radiotherapy.

O'Malley et al. [1] have demonstrated that intermediate energy photons (IEP), defined as photons with energy between ortho-voltage and

megavoltage, can improve dose distribution for stereotactic radiosurgery for small irradiation field sizes due to a dramatic reduction of radiological penumbra. With a figure of merit, the authors concluded that mono-energetic IEP beams between 200 and 400 keV can obtain the best trade-off between penumbra reduction and depth dose [1]. Using Monte Carlo simulations, Pignoland Keller have evaluated the relative contributions of secondary electrons and photon scattering to the penumbra region for various field sizes and mono-energetic photon beams (200, 400, 600, 800, 1000 and 2000 keV, and a standard 6 MV beam). Results showed that beams with effective energy in the 300 and 600 keV range provided significant advantages for multiple beam stereotactic irradiations of tumor less than 2 cm in diameter [11]. As shown in Fig. 1, photon only transport shows no significant difference on the penumbra of various energies, while for full Monte Carlo (MC) transport, the lower energy beams (200 and 400 keV) have much sharper penumbra compared to 6 MV beam.

2.2 Dose Fall-off and Exit Dose

For protons and other heavy ions, the dose increases first up to Bragg peak with increasing depth while particles penetrate the tissue. Beyond Bragg peak, the dose quickly drops to zero (e.g., protons) or almost zero (e.g., heavy ions) [12]. As such, less energy is deposited into healthy tissue surrounding the target. Unlike these particles, bremsstrahlung X-rays show a typical exponential decay with increasing depth. This fast dose fall-off is important when considering optimal dose distributions to the tumor as well as surrounding critical organs. Fast dose fall-off is beneficial to sparing healthy tissues downstream, especially for small tumors. However, it is not suitable for large tumors where homogeneity of dose distribution within the target will be compromised [3].

Usually the absorbed dose is described as percent depth dose (PDD), which is a function of beam energy, depth, field size, and source-to-surface distance (SSD). For the 10 cm x 10 cm field size, the dose fall-off of different energies is calculated as the percent dose decrease per cm between depth of maximum dose d_{max} and depth of half maximum, d_{50} . A special supplement of British Journal of Radiology [13] provides central axis depth dose data for use in radiotherapy departments from 2 MV to 50 MV. Buzdar et al.

have analyzed the depth dose characteristics of photons in water [3]. As summarized in Table 1, the photon dose fall-off rate beyond d_{max} decreases as beam energy increases. For example, the percentage dose of 2 MV photon beam reduces by 4.63% per cm while for 6 and 10 MV, the dose fall-off rates are much lower at 3.55% per cm and 3.18% per cm, respectively.

2.3 Dose to Bone

The predominance of Compton absorption in the megavoltage range is a definite advantage with respect to irradiation of healthy bone [10]. One of the concerns in using low energy photon beams for treatment is the increased absorbed dose in bone, due largely to the photoelectric effect. Laughlin et al. [10] have investigated the absorbed dose in tissue imbedded in bone relative to the dose in tissue as a function of photon energy. It is apparent that superficial X-rays have a very high bone-to-tissue dose ratio, which enhances the risk of bone necrosis. However, a gradual increase in bone absorption with increasing energy above 1.25 MeV indicates that the dose to bone will only increase slightly with energy (as shown in Table 2). Also the bone-to-tissue dose deposition ratio reaches a plateau in the MV range, suggesting that dose deposition to bone would not be a limiting factor in considering low energy megavoltage X-rays.

2.4 Penetration Power and Skin Dose

The penetration power and skin dose are thought to be the limitations of low energy photon beams. However, with intensity modulation in dose delivery, it has been shown that radiotherapy has become less restricted by the penetration power and skin dose of low energy X-rays [14,15]. Using multiple non-coplanar beams, the poorer penetration of low energy photons can be compensated efficiently, with deep-seated prostate cancer treated to high dose with 6 MV photon beams [1,15]. Also, multiple, non-opposing, and often non-coplanar beams or arcs, spreading in a large solid angle are widely used in the clinic nowadays in volumetric modulated arc therapy (VMAT) of cancers. Photon beams go through patient anatomy from multiple angles and hence dose delivery burden has been largely diluted. Superior target coverage is feasible without overdose of superficial tissues even with low energy X-ray beams [2].

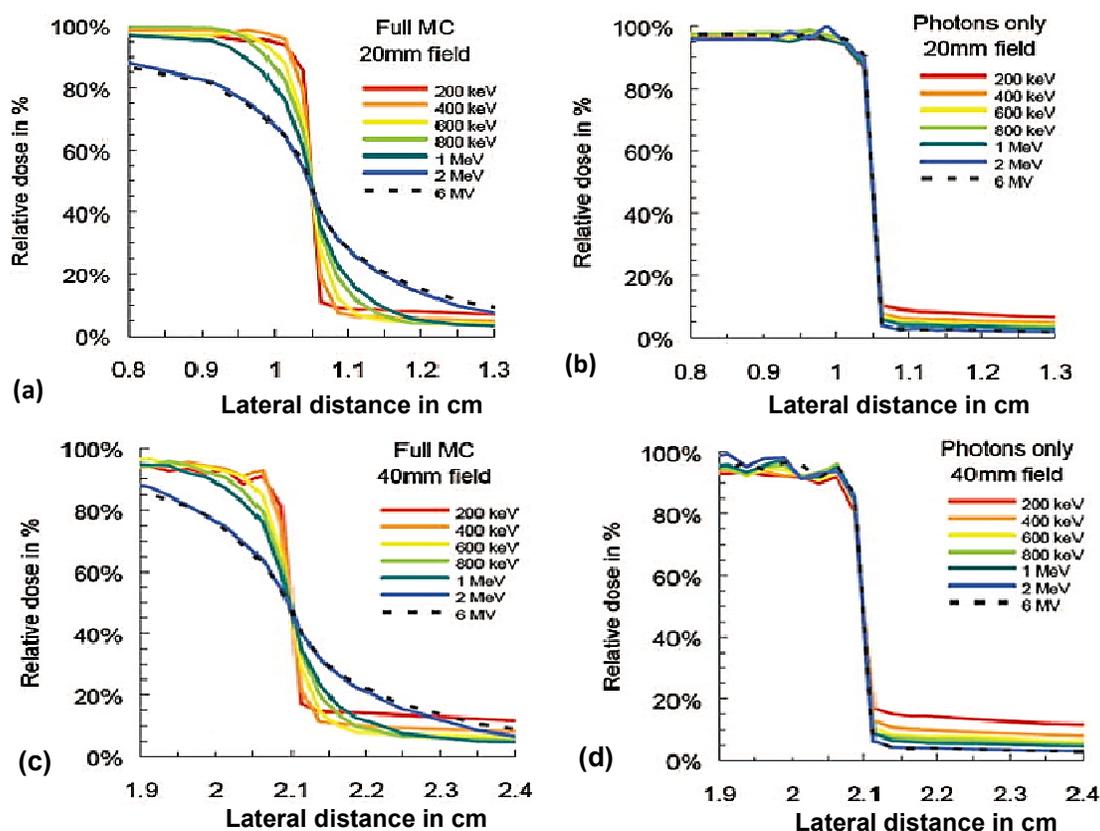


Fig. 1. Relative lateral dose curves for a variety of beam energies (200, 400, 600, 800, 1000, and 2000 keV mono-energetic photon beams, and a standard 6 MV beam) of 20 mm and 40 mm fields at 5 cm depth in water. The doses are calculated for combined electron and photon full Monte Carlo transport, or photon only transport. Permission to use this figure has been granted by the authors [11]

2.5 Image Quality

The high imaging dose and/or poor image quality have limited the use of megavoltage portal images and megavoltage cone beam CT (MVCBCT). Image quality at a given imaging dose is typically better for kilovoltage cone beam CT (kVCBCT) imaging system than MVCBCT [16] since in MV-range, X-ray image contrast is dominated by Compton scattering, rather than photoelectric interaction. In the diagnostic energy range (25-150 keV), as the attenuation coefficients of photoelectric effect depend strongly on the atomic number of absorbing material ($\propto Z^3$), it is possible to improve contrast between bone and soft tissue and subsequently improve image quality [12]. The response of most imaging devices, such as electronic portal imaging device (EPID), is typically optimized in the keV range [17]. In the therapeutic energy range, the low energy megavoltage X-ray beams

(1-4 MV), generated with low-Z electron targets such as aluminum, carbon and beryllium [4,18], will have much more low-energy photons in the keV range as compared to conventional 6 MV and higher energy photon beams. Hence, the more low-energy photons in the keV range, the better imaging device response and image quality.

3. THERAPEUTICAL APPLICATIONS OF LOW ENERGY MEGAVOLTAGE X-RAYS

3.1 Cobalt-60

In the past decades, Cobalt-60 teletherapy machines have largely been replaced by advanced linear accelerators for radiotherapy delivery. However, in recent years, Cobalt-60 source has been revived and applied in latest radiation therapy facilities [18,19].

Table 1. Dose fall-off characteristics for photon beams of different energies [3]

Beam energy [MV]	Depth of 100% dose (d_{max}) [cm]	Depth of 50% dose (d_{50}) [cm]	$D_{50}-d_{max}$ [cm]	Dose fall-off Rate* [cm ⁻¹]
2	0.4	11.2	10.8	4.63
4	1	13.9	12.9	3.88
5	1.25	14.5	13.3	3.77
6	1.5	15.6	14.1	3.55
8	2	17.2	15.2	3.29
10	2.3	18	15.7	3.18
12	2.6	19	16.4	3.05
15	2.9	20	17.1	2.92
18	3.2	21	17.8	2.81

* Average decrease in percent dose between d_{max} and d_{50}

Table 2. Dose in tissue imbedded in bone relative to dose in tissue as a function of accelerator voltage [10]

Machine	Nominal energy	D_{bone}/D_{tissue}
Superficial	100 keV	2.71
Co-60	1.25 MeV	1.03
Clinac-4	4 MV	1.04
Clinac-6	6 MV	1.05
Clinac-18	10 MV	1.06
Clinac-20	15 MV	1.07
Clinac-2500	24 MV	1.10

So far there have been several important modifications made on Cobalt machines. As listed in Table 3, one is the utilization of multi-leaf collimators (MLC) and implementation of inverse planning using modern 3D treatment planning system (TPS), which helps mitigate the defects such as relatively large penumbra and limited penetration in Co-60 machines [20]. Sahani et al. [21] have proposed a design of a secondary MLC for a tele-Cobalt machine and optimized its design features through Monte Carlo simulation. Several studies have demonstrated that comparable treatment plans can be achieved using a Cobalt unit when compared with a modern Linac [19,22]. Fox et al. [20] have compared X-ray photons (6/18 MV) with Cobalt-60 source and demonstrated that nearly identical plans can be achieved between Co-60 IMRT and 6 MV IMRT. Noticeably, a double-focused MLC has been employed to deliver radiation beams from Co-60 unit, with its penumbra comparable to that of a MLC in a Linac.

Helical tomotherapy employs a fan-beam radiation from a source mounted in a CT-like ring gantry. Complex conformal dose delivery can be achieved by modulating the intensity of radiation beams as the X-ray source revolves around the patient. Cadman et al. [23] have investigated the

plan quality and treatment times delivered with a Co-60 tomotherapy unit for clinical IMRT cases. Likewise, Dhanesar et al. [24] have also evaluated the conformal dose delivery potential of a Co-60 tomotherapy unit on a typical head and neck (H&N) phantom. Their results indicated that Co-60 tomotherapy is capable of providing the state-of-the-art conformal dose delivery in both phantom and clinical studies.

The growing and critical need for cancer care in developing countries has evoked a debate on what is the best solution to delivering high-quality radiotherapy treatments to cancer patients in those countries while maintaining a cost-effective and value-based health care model. Several groups have compared Cobalt-60 with Linac treatments in details and recommended Cobalt-60 units in developing countries in terms of power supply, maintenance cost and training requirements [18,25,26]. However, radiation safety and security risks associated with Cobalt-60 units remain to be a great concern not only in developing countries but also in developed countries due to potential radiological exposure to the general public.

Most recently, three Cobalt-60 sources were integrated with magnetic resonance imaging (MRI) for MRI-guided radiation therapy [27]. Due to compatibility issue with magnetic field, it is relatively easier to incorporate a Co-60 machine into a MRI unit than a high energy MV Linac. Particularly, the radioactive decay from Co-60 does not interfere with MRI operation and the double-focused MLC and IMRT optimization can mitigate the issues with penetration and penumbra. Furthermore, the surface dose is greatly lowered by the magnetic field sweeping away contamination electrons and high-contrast soft-tissue MRI delivers superior imaging with no radiation dose. This new MRI-guided

radiotherapy system represents one of the newly revived applications of low energy MV X-rays.

3.2 <4 MV X-rays

As discussed above, the low energy photons have narrower penumbra due to reduced secondary electron range. O'Malley et al. [1] and Keller et al. [8] have demonstrated through Monte Carlo simulations and experimental measurement that intermediate energy photon (in the range of 0.2–1.2 MeV) combined with small field sizes, produced a reduced radiological penumbra leading to sharper dose gradient, improved dose homogeneity and sparing of critical anatomy adjacent to target volume. Later on, this principle was applied to a multiple beam arrangement in a stereotactic head phantom. The improvement in dose gradient and homogeneity with low energy photons allows for a higher prescription dose while minimizing dose to adjacent critical structures in stereotactic radiosurgery treatments [28].

The intracranial stereotactic radiosurgery (SRS) has been recently expanded towards stereotactic body radiotherapy (SBRT) of small tumors located in extracranial sites such as lung, liver, pancreas and prostate. As discussed, the low energy photons are particularly suitable to treating small tumors with limited microscopic extension adjacent to highly critical structures. Dong et al. [2] investigated extracranial robotic intensity modulated radiation therapy using flattening filter free 2 MV X-rays. 2 MV X-ray dose calculation model was generated using Monte Carlo simulation and used for inverse 4 π non-coplanar planning. Three treatment plans using 30 non-coplanar beams, 6 MV, 2 MV and dual energy 2/6 MV were generated and compared for a head and neck, a liver, a lung, and a partial breast patient, respectively. The authors concluded that the 2/6 MV X-ray plans had the best dosimetry followed by 2 MV only and 6 MV only plans in terms of equivalent planning target volume (PTV) coverage and improved organs-at-risk sparing. Zhang et al. [29] have investigated the dosimetric improvements in lung SBRT treatment using 3 MV photon beams commissioned on a commercial treatment planning system based on Monte Carlo simulations. Dosimetric benefits of 3 MV were observed on small-sized patients compared to 6 MV plans in terms of comparable tumor coverage and considerably reduced doses to adjacent critical structures.

3.3 4 MV X-rays

When a medium containing an air cavity is irradiated with a megavoltage X-ray beam, the dose build-up/down effects occur, causing underdose on the target edge and overdose to the normal tissues, which makes accurate dose calculation difficult. It has been shown in several studies that the build-up/down effects increase with beam energy. Behrens [30] addressed the question of whether an energy lower than 6 MV is desirable based on measurements and Monte Carlo simulations. Their results suggest that if the build-up effect is of concern when target volume is in the vicinity of air cavities, 4 MV should be preferred over both 6 MV and 8 MV. This work also shows that the build-up effect in Co-60 is significantly smaller than that in 4 MV. Fischbach et al. [31] studied the feasibility of using 4 MV beams for chest wall treatment in post-mastectomy radiotherapy and compared it to a standard 6 MV radiation treatment. They concluded that the use of 4 MV photon beams is a good alternative for treating thoracic wall without the need to place a bolus on the patient. The main limitation of 4 MV beams is low dose rate.

The low dose rate issue can be resolved by removing flattening filter from the beam line. The higher dose rate expected from removal of the flattening filter has motivated investigations by a number of research groups [32,33]. Most recently, Stevens et al. [34] investigated the dosimetric effect of a 4 MV flattening filter free (FFF) Linac on lung tumor treatment. Due to removal of the flattening filter, low energy photon fluence increases. As a result, 4 MV FFF beam is softer than those from Linac with flattening filter. It is anticipated that the shallow build-up region of the 4 MV photon beam could help achieve improved dose coverage of lung tumors, particularly those located centrally, away from surrounding mediastinum tissue. Increased dose rates of up to 800 MU/min were recorded for open field (relative to 320 MU/min for filtered open fields) and reduced head scatter was inferred from output factor measurement. Lung patients in particular, benefit from higher dose rates achieved by FFF beams, resulting in shorter beam on time.

3.4 X-rays of Mixed Energy

Dual energies for cancer treatments have been pursued in the past few years [35-37]. Basically, energy for each portal was carefully chosen

based on patient's anatomy, tumor location and relative location of critical structures to the tumor. The advantages of both high (usually 10 MV or higher) and low energy (6 MV) beams are utilized for patient's benefits. Malhotra et al. [35] showed that for prostate cases, the mixed energy photons of 6, 10, 15 or 18 MV would be better in terms of integral dose than using either low or high energy photons alone. Park et al. [36] investigated the effect of mixing high- (15 MV) and low-energy (6 MV) photon beams on the quality of intensity-modulated radiation therapy (IMRT) plans for prostate cancer patients. Mixed energy IMRT plans have similar target coverage, improved organ-at-risk (OAR) dose and integral dose for deep-seated tumors. In a study by St-Hilaire et al. [37], beam energy was added as an optimization parameter in an automatic aperture-based inverse planning system. Their work demonstrated that energy optimization using 6 and 23 MV beams could produce plans of better quality with less peripheral dose and fewer monitor units (MUs) for deep-seated (e.g., prostate) and moderately deep-seated (e.g., lung) tumors.

The limited penetration power of photon beams of lower than 4 MV is disadvantageous when using them for treatment of relatively thick patients or tumor sites. Park et al. [38] proposed a cylindrical energy modulator with adjustable thickness of mercury along the beam axis to replace the flattening filter and to modulate the original 6 MV photon beam. The beam line was commissioned into a treatment planning system (TPS) based on Monte Carlo simulation to facilitate energy-modulated IMRT plans. The energy-modulated IMRT plans were shown to have less integral doses than 6 MV IMRT or 6 MV flattening filter free plans for tumors located in the periphery while maintaining similar quality of target coverage, homogeneity and conformity. In Dong's study [2], the authors concluded that the 2/6 MV dual energy plans had the best overall dosimetry followed by 2 MV only and 6 MV only plans. Zhang et al. [29] demonstrated that the 3/6 MV dual energy plans were superior dosimetrically among the three modalities for relatively thick patients on lung SBRT treatment. Recently, Zhang et al. [39] investigated the feasibility and impacts of mixed low energy photons (2-6 MV) on IMRT through Monte Carlo simulation. Instead of choosing energy for each gantry angle manually, the beam energy was determined with a newly developed energy selector which output the best energy for a specific gantry portal with minimal skin dose and

exit dose as well as maximal tumor homogeneity from a pool of photon energy beams (2 to 10 MV). Their results showed that the proposed method could offer a better paradigm for the radiotherapy of lung cancers and pediatric brain tumors in terms of normal tissue sparing and integral dose.

3.5 Pros and Cons of Low Energy Megavoltage X-rays for Therapeutic Applications

To summarize, the advantages of low energy megavoltage X-rays for therapeutic applications include:

1. The narrow penumbra can provide a tight dose distribution, especially for small fields;
2. The fast dose fall-off and low exit dose is good for adjacent structures sparing;
3. Low energy photons are suitable for small tumors and petite patients;
4. Mixed energy setting is advantageous towards personalized treatment;
5. It is relatively easy to lower photon energy without daunting technical modifications on current Linac, such as removing flattening filter [34], adding external device to modulate energy [38], reducing incident electron energy [2], and using low Z target material [40].

However, there are several limitations in employing low energy X-rays for therapeutic applications:

1. Low energy photons are not suitable for large targets, thick patients or very deep-seated tumors;
2. Low energy photons have a wider scattering angle, hence increased out-of-field scattering dose;
3. The radiobiological effects of low energy photons are still unknown;
4. Including low energy photon beams for radiation treatments would require extra workload for all the radiotherapy practitioners, including physicians, physicists, dosimetrists and technicians.

4. IMAGING APPLICATIONS OF LOW ENERGY MEGAVOLTAGE X-RAYS

Modern radiotherapy relies on routine applications of imaging procedures for accurate tumor localization, real-time patient setup and margin reduction in the radiotherapeutic

management of cancers, a technique known as image-guided radiotherapy (IGRT). Obtaining images with clinically acceptable image quality during the course of a radiation treatment can be especially beneficial in the situations where a lesion being treated is in soft tissue region and may move around or change in shape or position during the time span over which the treatment is delivered. On the other hand, as most of the imaging techniques in IGRT involve ionizing radiation, the imaging doses from these imaging procedures are of great concern.

4.1 Cobalt-60

As summarized in Table 4, using a tomotherapy bench top apparatus attached to a conventional Co-60 unit, Schreiner et al. have demonstrated that the modified Co-60 unit can be used for not only conformal dose delivery but also megavoltage computed tomography imaging [41,42]. The developed Co-60 MVCT imaging techniques can provide adequate image quality required for IGRT.

4.2 X-rays of Discrete Energy

Recently, several groups have dedicated to modifying therapy beam line to get low energy photon beams (≤ 4 MV) for imaging. They all considered thin, low-Z targets with electron energies as low as reasonably achievable on current radiotherapy Linacs. Faddegon et al. [17,43] introduced a modification to a Siemens Oncor Linac using a 1.32 cm thick carbon target with 4.2 MeV incident electrons. The lower energy X-rays can generate images of the same quality with less than one-third of the dose compared to a 7.0 MV treatment beam line. Beltran et al. [44] have measured the dose-CNR response and compared the imaging dose on a cohort of pediatric patients for imaging beamline CBCT versus standard treatment beamline orthogonal port films. The former delivered approximately one-fourth doses as compared to conventional ortho-pair films. Similarly, Roberts et al. [45] used a 2 cm thick carbon target placed in an Elekta Precise Linac operating at 4 MeV electron mode with primary and secondary scattering foils removed. This work showed that the megavoltage planar image contrast of dense bone in water was improved by a factor of 4.62 for thinner phantoms (5.8 cm thickness) and by 1.3 for thicker phantoms (25.8 cm thickness). Spatial resolution was improved when compared to 6 MV therapy beam. Robar et al. [5] installed an aluminum target in a Varian 2100EX Linac.

Megavoltage imaging beams were generated using either 3.5 or 7.0 MeV electrons, which offered clear advantages over standard 6 MV therapy beam in terms of improved contrast-noise ratio (CNR). The CNR was increased by a factor of 2.4 and 4.3 for 7.0 and 3.5 MeV beams, respectively.

4.3 Megavoltage Fan Beam CT

The megavoltage fan beam CT (MVFBCT) with nominal energy of 3.5 MV from commercial Helical Tomotherapy units has also shown sufficient contrast for soft-tissue delineation for clinical IGRT [46,47]. Parsons and Robar [40] further lowered the incident electron energy to between 1.9 and 2.35 MeV and assessed the improvement of megavoltage planer image quality with the use of carbon (7.6 mm thickness) and aluminum (6.7 mm thickness) LINPAC target. Their work has demonstrated that CNR has improved by factors ranging from 3.7 to 7.4 as compared to a 6 MV therapy beam when the beam energy was lowered below 2.35 MeV with a large fraction of kilovoltage X-rays in the beam, ranging from 46% to 54%.

4.4 X-rays of Variable Energy

Roberts et al. [48] investigated the effect of low energy photon beams on image quality using a novel waveguide test piece, in which a variable coupling device (rotovane) was installed to generate a wide range of continuously variable energy between 1.4 and 9 MeV suitable for both imaging and therapy. The imaging beam consists of 1.4 MeV electrons incident on a water-cooled electron window made up of stainless steel, a 5 mm carbon electron absorber and 2.5 mm aluminum filtration, providing high contrast images from therapy portal at low dose. The imaging dose to obtain the same quality images was shown to be 12 times higher than a 100 kVp CBCT system (Elekta XVI), but 140 times lower than a 6 MV cone beam imaging system.

4.5 Pros and Cons of Low Energy Megavoltage X-rays for Imaging Applications

Using low energy megavoltage X-rays for imaging is advantageous for the following reasons:

1. It allows for better tumor motion management as beam's-eye-view images

- and target tracking can be achieved simultaneously during radiotherapy treatment. Markerless EPID tracking using therapeutic MV exit beam has been proved to be favorable compared to implant-based KV tracking approaches [49-51]. Besides, for robotically mounted Linac, the reduction in weight and size of the Linac with the use of low energy MV X-rays helps increase the flexibility and accuracy in tumor tracking [2].
- Another distinct advantage of MV imaging is that image quality is maintained even when high atomic number materials such as tooth fillings, dental implants, surgical clips, fiducial markers, or hip replacements are present. For kV imaging, metallic objects would create severe artifacts, thus MVCBCT images can be used to assist in segmenting CT imaging with metal artifacts for treatment planning purpose [47,52-55].
 - Since the MV imaging source is modeled in the treatment planning system (TPS), daily MV portal/MVCBCT imaging dose can be managed efficiently through TPS dose calculation and incorporated into treatment plans [56,57].
 - With improved image quality or reduced imaging dose, MVCBCT-based dose-guided radiation therapy [58,59] and in-vivo dosimetry [60,61] are becoming increasingly attractive.

Table 3. List of key works investigating therapeutic applications of low energy X-rays

Energy	Key References	Subjects	Conclusions
Co-60	Van,1996 [18], Warrington,2002 [19] Sahani, 2013 [21]	Cobalt teletherapy unit Cobalt teletherapy unit	A revived treatment modality A design of a secondary MLC ¹
	Fox, 2008 [20] Adams, 2008 [22]	Co-60 IMRT	Comparable quality in treatment plans
	Cadman, 2011 [23], Dhanesar, 2013 [24]	Co-60 Tomotherapy	State-of-the-art conformal dose delivery
	<4 MV	O'Malley, 2006 [1] Keller, 2007 [9]	Simulations of IEP ² Experiments of IEPs
	Keller, 2009 [28]	1 MV X-rays;	Improve dose gradient, conformality, and homogeneity for SRS ³
	Pignol, 2009 [11]	Mono x-rays (≤ 2 MeV)	Secondary electron range is the main contributor to radiological penumbra
	Dong, 2014 [2]	2 MV FFF ⁴ X-rays	Equivalent PTV coverage and improved OAR ⁵ sparing from 2 MV plans
	Zhang, 2014 [29]	3 MV X-rays	Improved dose distribution on lung SBRT ⁶ plan
4 MV	Behrens, 2006 [30]	Dose build-up for Co-60, 4, 6 and 8 MV	4 MV is preferred over both 6 MV and 8 MV when target is in the vicinity of air cavities
	Fischbach, 2013 [31]	4 MV vs 6 MV beams	4 MV is a good alternative to treating thoracic wall without a bolus
	Stevens, 2011[34]	4 MV FFF beam	Increase dose rates of around 800 MU/min Improve dose distribution for lung treatment
Mixed energy	Malhotra, 2005 [35]	Mixed 6, 10, 15, 18 MV	Reduce ID ⁷ for prostate cases
	St-Hilaire, 2009 [37]	Energy optimization using 6 and 23 MV	Less peripheral dose and fewer MUs for both prostate and lung cases
	Park, 2011[36]	Mixed 6 and 15 MV	Improve OARs dose and ID for prostate
	Park, 2012 [38]	Adjustable Energy	Less integral doses for peripheral tumors
	Dong, 2014 [1]	Mixed 2 and 6 MV	Best overall dosimetry
	Zhang, 2014 [29] Zhang, 2014 [29]	Mixed 3 and 6 MV Selected from 2-10 MV	Superior dosimetrically for thick patients A better paradigm for lung and brain tumors

¹Multi Leaf Collimator; ²Intermediate energy photons, 0.2-1.2MV; ³Stereotactic radiosurgery; ⁴Flattening filter free; ⁵Organ at risk; ⁶Stereotactic body radiotherapy; ⁷Integral Dose

Table 4. List of key references investigating imaging applications of low energy X-rays

Key references	Modifications	Major results
Faddegon, 2008 [17]; Faddegon, 2010 [43];	1.32 cm thick carbon target with 4.2 MeV electrons incident to a Siemens Oncor Linac	Improved image quality with less than one-third dose as compared to a 7 MV beam
Beltran, 2009 [44];		Reduced CBCT imaging dose on pediatric patients by a factor of 4 as compared to ortho-pair films
Roberts, 2008;	2 cm thick carbon target with 4.0 MeV electrons incident to an Elekta Precise Linac	Planar image CNR increased by a factor of 4.62 and 1.3 for thin and thick phantom as compared to 6 MV therapy beam
Robar, 2009 [45];	1.0 cm/0.67 cm thick aluminum target with 7.0 MeV /3.5 MeV electrons incident to a Varian 2100EX Linac	CNR increased by factors of 2.4 and 4.3 for 7.0 and 3.5 MeV, respectively for CBCT and planar imaging as compared to 6 MV
Yartsev, 2007 [46]; Chan, 2011[47];	Photons of 3.5 MV nominal energy for imaging in Helical Tomotherapy units	Sufficient contrast for soft tissue delineation for clinical IGRT
Parsons, 2012 [40];	0.76 cm thick carbon and 0.67 cm aluminum targets with incident electrons of 1.90 to 2.35 MeV	CNR improved by factors ranging from 3.7 to 7.4 compared to a 6 MV therapy beam
Roberts, 2012 [40];	Continuously variable energy between 1.4 MeV and 9 MeV	Imaging dose of 1.4 MeV beam was 12 times higher than a 100 kVp CBCT system (Elekta XVI), but 140 times lower than a 6 MV cone beam imaging system
Schreiner, 2003 [42]; Schreiner, 2009 [41];	Co-60 unit (1.25 MV) Co-60 Tomo unit (1.25 MV)	Adequate image quality required for IGRT

However, it should be noted that the image quality of megavoltage beams is still worse than that of kilovoltage beams. Although low energy MV beams have been proved to improve the image quality in term of CNR, the spatial resolution and contrast of soft tissues remain to be two major limitations to MV beams for imaging applications. How to generate low energy photon beams (≤ 4 MV) without dramatic mechanical modification required to current treatment machine is an important and challenging issue. Current studies have been focused on optimization of photon spectrum by means of optimizing target material, thickness and electron filter thickness. The optimal target design for imaging is still undergoing.

5. CONCLUSION

A review of recent progresses on low energy megavoltage X-ray beams (1-4 MV) in the applications of radiotherapy and radiological imaging has been presented. On the one hand, with narrow penumbra and low exit dose, low energy megavoltage X-rays have been found suitable for radiation treatments of small tumors and petite patients. However, they are not sufficient for deep-seated tumors or large

anatomy due to their limited penetration power. On the other hand, low energy megavoltage X-rays can be useful in reducing metal artifacts, unifying radiotherapy and imaging with one single beam and improving CNR. But their spatial resolution and soft tissue contrast are still inferior to those of kilovoltage X-rays.

6. FUTURE OUTLOOK

So far, all the current investigations on low energy MV X-rays for treatment or imaging during cancer radiotherapy have been focused on technical development and feasibility study. Usually technical development involves modifications to current Linacs or Co-60 units so that low energy MV X-rays can be generated for clinical treatments or imaging. The results of feasibility study are often derived from a limited number of clinical cases treated with a certain low energy photon beam, whose conclusion would need to be validated with more comprehensive studies collectively.

Looking forward, low energy megavoltage X-rays can be very useful in the future in two important developments: Personalized radiation treatment [62] and personalized imaging protocols [63].

With more energy options available for a full range of energy optimization and with consideration of lesion site, anatomy, treatment history and clinical needs of each patient, the treatment plans will be more superior dosimetrically and more personalized with better treatment outcome. In addition, with a single low energy megavoltage X-ray beam for not only radiation treatment but also imaging, cancer radiotherapy will become much more efficient and accurate. To do that, tailoring imaging parameter setting according to specific patient needs would be the key to reducing harmful radiation dose and improving image quality in the complex management of cancers using radiotherapy. Further technical developments and more clinical data would be needed to warrant widespread applications of low energy megavoltage X-rays in cancer radiotherapy. In particular, more efforts would be required to understand the biological effect of low energy megavoltage X-rays for more tailored and improved radiation treatments of cancer patients.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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