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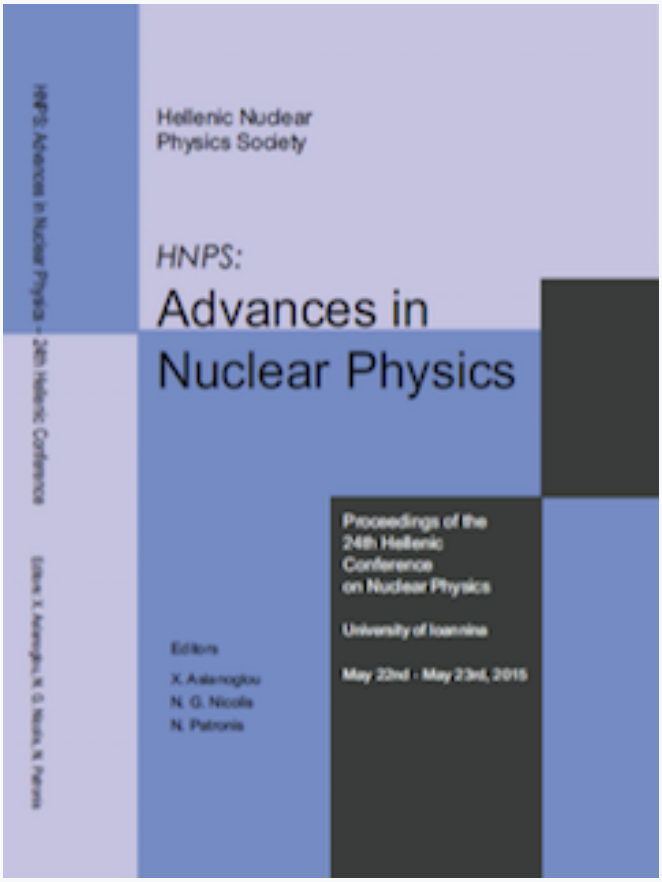

A rebirth of radiation therapy with kV X-rays?

J. Kalef-Ezra

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A rebirth of radiation therapy with kV X-rays?

John A. Kalef-Ezra

Medical Physics Laboratories of the University of Ioannina School of Health Sciences and the Ioannina University Hospital, 451.10 Ioannina, Greece

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Abstract

Novel clinical approaches using kV X-ray beams are currently under study, such as selective dose enhancement in malignant tissues due to the enhanced presence of atoms with high atomic number, Z, in tumors relative to normal tissues or the use of heavily spatially fractionated kV X-ray irradiation.

Local dose enhancement by high Z atoms: A substantial dose gradient between normal and malignant tissues can be achieved by biologic targeting the cells to be "destroyed" with high Z atoms and its irradiation with photons in the energy region of tens of keV, such as synchrotron produced X-rays of energy above the K-edge. The selective accumulation of high Z atoms can be achieved by various techniques, such as by intravenous administration of a) contrast enhancement agents, b) some chemotherapeutic drugs c) nanoparticles and d) DNA precursors loaded with Z-atoms. Taking into account the limited availability and the high cost of GeV synchrotrons, brachytherapy sources could be used.

Microbeam radiation therapy: Studies carried out in experimental models using spatially micro-fractionated beams have shown drastically elevated tissue radiation tolerance, with higher tissue sparing in healthy tissues than in malignant ones. This phenomenon is attributed by some investigators to the proliferation and migration of cells from the "low" dosed regions (~10 Gy) to the adjacent "heavily" dosed regions (many hundreds of grays). Multi-slit collimators allow for the production of X-ray microbeam arrays at 3rd generation synchrotron units. Monte Carlo simulations were tested versus direct dose measurements. Promising preclinical studies carried out so far, trigger studies on the development of alternative less expensive technologies.

Key words: synchrotron radiation, radiation therapy, microbeam, photon activation therapy

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INTRODUCTION

About 1/3 of Greeks are going to develop cancer at some time in their life. Moreover, 28.000 deaths are attributed annually in Greece to cancer. Although the exact mechanisms believed to underpin the biological response of the human body to high doses of ionizing radiation are still uncertain, radiation therapy is one of the main means in cancer treatment. Radiation therapy (RT) is used either alone or as a part of a multidisciplinary approach as a curative modality in about 30% of the patients with solid tumors and in another 25% as a palliation one. It involves treatments with external beams of ionizing radiation (teletherapy), sealed and unsealed brachytherapy sources. When successful, RT cures by eradicating tumor in the primary site and draining regional lymphatics and lymph nodes, usually by reproductive death. A number of additional disorders are also treated with ionizing radiations, such as hyperthyroidism and some types of focal neurological lesions.

In conventional RT, radiation beams aim toward the target delivering a high dose to the target in an attempt to control the disease with tolerable collateral damage to vital health tissues inevitably irradiated. Typically, a total dose between 40 and 90 Gy is absorbed to the clinical target volume to treat malignant

tumors with curative intent with temporary fractionated MV X-rays and/or electron irradiations (typically a ~2 Gy tumor dose with a single fraction 5 days per week) and much lower doses (e.g. 15 Gy) in the case that the dose is given in one or just few fractions.

Despite research efforts and large amounts of money spent to develop sophisticated treatment techniques, such as the use of tighter radiation fields by increased accuracy in the irradiation of the target or the use of hadron beams, limited enhancement in the clinical outcome was achieved in some tumor types during the last 20 y. As maximal tumor dose is restricted by healthy tissue tolerance, increase in target dose is usually unfeasible due to the increase of adverse effects in healthy tissues. Therefore, in some solid tumor types with poor response to the currently available treatment modalities, such some lung and brain tumors (e.g. multiple glioblastoma), only palliative therapies can be applied that offer some limited extend in survival or/and improvement in quality of life. For his reason novel clinical approaches usin, among other thing kV X-ray beams, are currently under study, such as via dose enhancement in malignant tissues irradiated under higher concentration of atoms of high atomic number, Z, in them relative to the neighboring healthy tissues (physical approach) or by the use of heavily spatially fractionated radiation beams (biological approach).

LOCAL DOSE ENHANCEMENT BY HIGH Z ATOMS

Most solid tumors grow rapidly and have metastatic potential to distant sites. To sustain their rapid growth rate most of them exhibit increased vascularity and highly enhanced blood vessel permeability [1,2], characteristics that can be clinically exploited. A substantial dose gradient between normal and malignant tissues, such as in glioblastoma multiforme, meningioma and brain metastasis, can be achieved by biologically targeting the tumor cells with atoms of Z>~50, such as I, Gd, Pt and Au and irradiating them with photons in the energy region of many tens of keV. More specifically, photo-electrons, Auger and Coster-Kroning electrons following photoelectric interaction with high Z atoms increase the energy imparted at sites close to the interaction point, due to their short range (e.g. csda ranges of 2, 12 and 42 μm in water of 10, 25 and 50 keV electrons, respectively, values comparable with the ~20 μm "average" diameter of human cells). The selective accumulation of such atoms in a tumor can be achieved by increased tumor uptake of intravenously administered contrast enhancement agents (such as iodinated and gadolinium contrast agents widely used in radiology to enhance the visibility of vascular structures and organs during X-ray and MRI imaging, respectively), platinum as cisplatin (a drug widely used in chemotherapy) and metallic nanoparticles, such as Au nanoparticles. An alternative root is the administration of compounds used in DNA synthesis and tagged with high Z atoms. Taking into account the limited availability and the high cost of powerful synchrotrons, permanently implantable brachytherapy sources (e.g. ^{103}Pd, ^{125}I and ^{145}Sm seeds), could be used as photon sources, provided that the high Z atoms are present onsite over adequate time period [3,4].

1.a Contrast-enhanced synchrotron stereotactic radiotherapy (CESSRT) is based on the preferential uptake in some tumor types of compounds loaded with iodinated and gadolinium contrast agents and the stereotactic irradiation of the target with X-rays of energy that compromises between high photo-electric cross section in the high Z atoms and adequate penetrability in the human body. The successful outcome of studies carried out either *in vitro* or in small animals, such as in rats bearing F98 glioma, as well as in eight patients with metastatic brain tumors combined with the development of a appropriate dosimetric and treatment planning methods lead to a CESSRT clinical trial [5-9]. More specifically, a study was initiated on June 2012 at the European Synchrotron Radiation (ESRF) facility in Grenoble (France) to test CESSRT feasibility and safety. For this purpose a dedicated treatment room has been built at ESRF,

equipped amongst other things, with an armchair where the patient's head is tightly maintained by a stereotactic frame. Quantitative computed tomography is used to measure iodine concentration in the irradiated structures (typically ~1.5 mg/g in tumor over a 30 min long time-period). Besides the high construction and running costs of such a facility, the irregular uptake of the contrast agent in the tumor at both macroscopic and microscopic level (present primarily in the extracellular space and very low in the tumor necrotic regions, if any) is an additional disadvantage of this clinical approach.

1.b Nanoparticles are known to permeate leaky angiogenic endothelium, resulting in higher particle concentration in many tumors than in the surrounding healthy tissues, an effect that could be used therapeutically. For example, a 42 Gy single X-ray irradiation of mice carrying highly aggressive, radiation-resistant SCCVII subcutaneous squamous tumors in their thighs with a 68 keV median X-ray beam at the Brookhaven National Laboratory, BNL (Upton, New York, USA) increased by almost three times the long-term survival of tumor bearing mice previously injected intravenously with Au nanoparticles (1.9 nm in diameter) versus mice irradiated with no nanoparticles in place [10]. Similar tumor control efficacy was achieved by a lower dose, 30 Gy, given in one or two fractions under Au nanoparticle presence, following hyperthermia. Note that the nanoparticles, as given (1.9 mg of Au per g body mass) had no apparent short or long-term toxic effect and resulted in a 7 mg g^{-1} mean Au concentration in the tumor at the irradiation time.

1.c Some microdosimetric studies indicated that the critical cellular structures relevant to acute radio-biological effects have sizes in the range 6-10 nm, which is comparable to the diameter of individual DNA strands. Therefore, the biological efficacy of kV X-rays is anticipated to be higher in cases that the high Z atoms are taken-up in the nuclear DNA molecule. Therefore, in Photon Activation Therapy (PAT), proposed by R. Fairchild back in 1982, aphoton irradiation above the K-edge is carried out following the administration of an iodine incorporated to a thymidine analog in DNA, such as iodinated deoxyuridine, a [11,12]. By that time, other compounds that also may carry high Z atoms to the nuclear DNA were proposed for use, such as Pd-loaded porphyrins [3].

MICROBEAM RADIATION THERAPY

Microbeam radiation therapy (MRT) is a novel, preclinical modality for cancer treatment and brain radiosurgery, invented in 1992 by D.N. Slatkin *et al* at BNL [13]. MRT is based on the fine spatial fractionation of the absorbed dose to the irradiated tissues, that allows the delivery of high doses to well defined microscopic sections within a short time (dose rates of at least many 10^2 Gy s^{-1} in case that adequate triggering is not available), while sparing the adjacent healthy tissues. For example, the production of X-ray beams collimated to micrometer scale (microbeams) and separated by wider spacing, requires a minimally divergent beam that passes through an appropriate micro-collimator. X-rays of energy higher than about 250 keV round substantially the lateral dose deposition profile due to the substantial range of the ejected Compton electrons (e.g. csda range of 143 μm in water, in case of 100 keV electrons), thus decreasing the peak to valley dose ratio (PVDR). Therefore, photon spectra with median energy in the region of 100 keV usually offer the best compromise between sharp dose gradients and adequate beam penetration in the human body.

The requirements of extremely high dose-rates coupled with the minimal X-ray beam divergence are currently met only by the 3rd generation synchrotron sources. More specifically, the radiation produced in their wiggler magnets, allow the absorption of extremely high doses along the penetration path with small dose dispersion, resulting in negligible dose blurring due to organ motion (e.g. brain moves

periodically up to ~100 μm with velocities up to ~2 mm s^{-1} due to perfusion and diffusion). Such "white" beams, after appropriate filtration to reduce the low energy spectral component (e.g. 1.5 mm of Al plus 1.0 mm of Cu), are spatially fractionated into microbeams by an adequately cooled multi-slit collimator [14,15], producing an array of quasi-parallel microbeams. The heavily irradiated zones (e.g. peak doses in 20 to 80 μm- thick zone of many hundreds of Gy) are separated with wider zones of much lower dose (~10 Gy valley zone, 30 to 320 μm- thick) with a sharp transition zone between them. Such microbeams deliver extremely high doses of radiation to the cells along their paths, up to some depth and much lower doses to the adjacent cells generating thin quasi –surgical cuts
(note that the median size of human cells is about 15 μm).

Dose distribution predictions by Monte Carlo simulations have to be tested versus direct measurements before any clinical trial. The dynamic range of dose measurements in MRT is wide (10^0 to 10^3 Gy) and the dose rates up to five orders of magnitude higher than those used in conventional teletherapy (usually not exceeding 0.1 Gy s^{-1}). In addition, the high dose gradients require accurate measurements on microscopic volumes, something which is not required in conventional teletherapy, where dose mapping is usually carried out with ionization chambers with effective volumes ~0.1 cm^3. Therefore, either pre-existent dosimetric methods had to be adopted accordingly or new methods had to be developed for both homogenous and spatial fractionated fields. Among other things, radio-chromic films, chemical dosimeters (e.g. Fricke and bang gels and radiochromic PRESAGE dosimeters), MOSFET detectors, multiple Si-based detectors and two-dimensional thermoluminescent dosimeters (TLDs), were tested as potential dosimeters to validate planned dose distributions.

Some of the dosimetric techniques that could be applicable in MRT were recently reviewed within the EU SYRA3 COST Action TD1205 [9]. For example, the beamline output of the biomedical ESRF ID17 therapeutic is currently routinely assessed by fast scanning of a pin-point ionization chamber with constant velocity in front of the beam-port. An experimentally determined correction factor due to the substantial electron-ion recombination is applied to the thus obtained values. Such measurements are backed by calorimetric ones [17]. Earlier, the doses in soft tissue stated by Dr Avraham Dilmanian and colleagues at the 2.8 GeV National Synchrotron Light Source at BNL in a number of studies during the period 2000-2009, were independently tested several times at the University of Ioannina (U.I.) using two independent dosimetric techniques in each experimental run. More specifically, radiochromic films (MD55-2 or H810) and LiF:Mg,Ti TLDs were scanned with a constant velocity across the beam-port. For calibration purposes, both films and TLDs were irradiated at U.I. using either a 6 MV medical linear accelerator or ^{60}Co sources and were read together with those irradiated at BNL. Correction factors were used, among other things, for differences in the irradiation to read-out time intervals, detector non-linear dose response and energy response. The ratio of the measured to the anticipated doses using various filtration schemes (0.25 to 12.7 mm of Cu to modify the X-ray spectrum) and irradiation geometries (e.g. field sizes, measurements either free in air or in phantoms) ranged between 0.92 and 1.17.

A number of studies on experimental models, such as flies, mice, rats, ducks, chicken, rabbits and piglets [18-25] irradiated at either BNL or at ESRF with X-ray microbeams with spectra peaking between 50 and 130 keV, indicated extraordinary high tolerance of normal tissues following a single irradiation fraction (doses of many hundreds or even thousands of Gy along the microbeam paths) relative to uniform irradiation fields of identical size. However, lower tolerance enhancement was observed in tumors [25-34], indicating for a potential wide therapeutic dose-window.

The enhanced radiation tolerance to microbeams is attributed by some investigators to abscopal effects, i.e. proliferation and migration of cells from the "low" dosed regions to the adjacent "heavily"

dosed regions. This mechanism seems to be more effective in healthy tissues than in malignant ones, provided that the width of the heavily irradiated zone is of a size that allows the neighboring cells in the valley zone to induce "healing". For example, some researchers claim that the normal tissue sparing of the central nervous system is related to the resistance of the mature vascular network (vascular endothelial cells) to microbeam irradiation, whereas the immature network cannot repair so efficiently the radiation induced damage, (e.g. denudation of capillaries), resulting to reduced tumor perfusion and finally to decrease in the number of tumor vessels [22,25].

In principle, one could anticipate improved curative outcome by MRT exposures from different directions. However the accurate cross-firing alignment of microbeams is problematic, mainly due to the heart beat that moves the target position in space. In addition, the PVDR decreases with increasing photon energy and increasing radiation field size in a specific spatial fractionation scheme. Therefore, MRT is not anticipated to be appropriate for the treatment of large or/and deep sited targets due to poor beam penetration [16].

In conclusion, MRT studies carried out on small animal models have shown that MRT could be a promising method that might be applied to patients with malignant tumors and some focal neurological lesions (e.g. drug-resistant epileptic foci) that cannot be treated satisfactory with the currently available means [35]. However, experiments in larger animals bearing spontaneous tumors, such as dogs and cats with dimensional and physiological similarities to those of human malignancies, should be carried out before proceeding to the clinical trials [35]. Meanwhile, studies are underway to develop alternative compact and less expensive X-ray sources that could replace synchrotrons in clinical practice, such as sources based on carbon nanotube field-emission [36] or on the inverse Compton scattering effect that takes place during the collision of a high energy electron beam with a powerful laser beam [37]. Thus, kV-X rays may come back to the daily clinical therapeutic practice.

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