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Role of synchrotron radiation in cancer: A review on techniques and applications

Abstract

In spite of the scientific and technological advancement of radiotherapy over the past decades, only calming therapy is accessible for high-grade cancer tumors. This often only extends the survival of individual patients by a few months. During the last three decades, many research groups have carried out experiments and trials to develop novel imaging and radiotherapy techniques for cancer treatments, based on the use of synchrotron X-rays. There are numerous synchrotron biomedical stations around the world, which put forward an admirable platform to improve either the radiotherapy treatment or imaging diagnosis for various cancer tumors. Synchrotron radiation with exclusively biological and physical advantages might signify an inventive approach for cancer treatment. In this time, various Synchrotron radiation-based photon activation therapies have been developed, and the results of in vitro and in vivo experiments are very promising. It is essential to comprehend the physical and radiobiological principles of novel strategies before these are applied at the clinical level. In this paper, we summarize the various techniques in terms of physical and biological and their applications.

Keywords: radiotherapy, synchrotron radiation, imaging diagnosis, photon activation therapies

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Introduction

Chemotherapy, surgery, and radiotherapy are the well-known modalities used for cancer treatment. As the discovery of X-ray in 1895 by Wilhelm Conrad Rontgen's, X-ray has been extensively utilized in the diagnosis and cancer treatment.[1,2] The radiotherapy has been swiftly tailored to the alleviation of cancer and plays a vital role in 60−70% of cancer patient cure. The existing procedure of radiotherapy, like conventional MV X-ray radiation therapy, still has restrictions in stipulations of physical and radiobiological characteristics. Hence, it is essential to building up new techniques to maximize the dose deposited in pathological tumor tissue attempting to whereas minimize radiation injuries to the surrounding normal tissues of the body.

In the last three decades, various research groups have carried out experimentations and trials to develop novel imaging and radiotherapy methods in cancer therapy, based on the utilizing of synchrotron X-rays. The arrival of synchrotron radiation (SR) has unlocked a novel alternative to the radiotherapy. SR is electromagnetic radiation, similar to cyclotron radiation, but generated by the acceleration of ultrarelativistic electrons through magnetic fields. This may be achieved artificially by storage rings in a synchrotron, or naturally by fast-moving electrons flying through magnetic fields in space. Electrons are accelerated to high velocities in several stages to achieve a final energy that is typically in the GeV range.

SR or synchrotron light combines enormously high photon beam strength, small noticeable source size, high collimation, tunability and a continuous energy spectrum i.e. from the far infrared (IR) region up to hard X-rays. These properties make SR a distinctive and helpful tool for biomedical imaging and therapy as shown in Figure 1.[2] SR facilitates the development of completely new X-ray imaging techniques, which take advantage of extraordinary sources of image contrast.

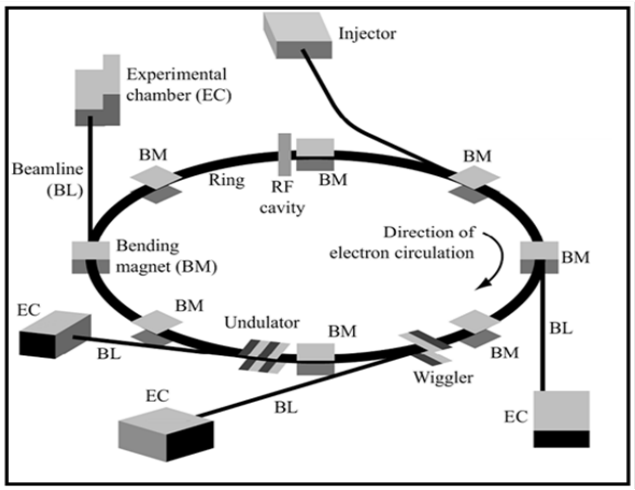

Figure 1 An overview Synchrotron radiation in cancer treatments and diagnostics.

While conventional radiography makes images via the differential absorption of X-rays through the tissues, but synchrotron-based imaging techniques may also produce high-resolution images using differences in the refraction and scatter of X-rays. Additionally, the high brightness of SR permits tuning the energy to narrow bands with the aid of monochromators (the energy band can be selected precisely, with a resolution of about 1eV), when keeping a very high photon flux.[2] Images of great contrast at relatively low doses can, as a result, be achieved in synchrotrons.[3,4]

The very high intensity and high-quality collimation of synchrotron X-rays also facilitate new methods of radiation remedy that cannot be attained at the moment with any other type of X-ray source. Some of these techniques have established to have great potential for the healing of cancer.[5,6] One of the major problems of conventional radiotherapy is the high dose deposition of radiation on the surrounding healthy tissues, higher than the tissue tolerances. Thus, it is essential to minimize the normal tissue dose deposition, while maintaining the dose delivered to the tumor.[7–9] So, synchrotron-based radiotherapy can be a promising therapy which delivers the very accurate irradiation of tumors by using a very high dose rate up to thousands of Grays (Gy) in a few milliseconds.[10]

Radiotherapy techniques

There are numerous synchrotron biomedical stations around the world, which put forward an outstanding stage to get better either the imaging diagnosis or radiotherapy treatment for diverse tumor types. In this, emphasize the results of a few of the strategies and techniques that have been developed at different biomedical synchrotron stations. There are various types of radiation therapies have been developed for the treatment of different types of cancer tumor. The first irradiation mode is based on a polychromatic beam spatially fractionated in micro (MRT) The second radiation mode uses a non-fractionated monochromatic beam (SSRT). Shanghai Synchrotron Radiation Facility (SSRF), a third-generation of synchrotron radiation light source commissioned in 2009, would be an invaluable tool for cancer treatment.

Microbeam radiation therapy (MRT): physical characteristics

The working principle of this method is that the radiation destroys that induces tissue necrosis may be significantly diminished by spatial microfractionation of the absorbed high dose of microbeams. It was started at the National Synchrotron Light Source (NSLS) at Brookhaven National Laboratory and is presently being pursued at the ESRF (Grenoble, France) and at Spring8 (Japan). Microbeam radiation therapy (MRT) is a system using highly collimated, quasi-parallel cross-planar or co-planar arrays of highly powerful microbeams created by a synchrotron. In order to accomplish this array, the beam is split by collimators into many parallel and planar beams in the 50–150keV energy range. The production of such microbeams, which is usually between 25 and 100μm full widths at half maximum (FWHM) values and 100-400μm center-to-center spacing, needs a multi-slit collimator either with fixed or modifiable microbeam width. The smallest dose in the central region between two microbeams is called the "valley dose.", while the maximum dose level called as "peak dose" is in the overlap area of microbeams. The peak and valley dose ratio in the irradiation field is thought to be of significance for the therapeutic outcome of the treatment and strongly depends on the assortments of parameters for example sample size and composition, X-ray spectrum, irradiation field and depth, the distance between peaks, etc. The peak and valley dose ratio is an important parameter that has to be optimized in MRT.[11–13] MRT can only be achieved with synchrotron X-rays due to their extraordinarily high flux density and small divergence which makes it sharply defined beam edges deep in the body.

Biological characteristics of MRT

MRT irradiation is usually based on a single fraction of radiation dose conveyed either uni-directionally or bi-directionally (co- or cross-planar) and distributes the alike benefit as Stereotactic synchrotron radiation therapy (SSRT) in terms of the radiobiological effect of hypo-fractionated irradiation. Additionally, peak entrance doses of several hundreds of Gy are incredibly well tolerated by normal tissues. Various experiments have been performed on different animal models such as mice, duck embryos, piglets, rats and rabbits and results indicated a meticulous resistance of normal tissues to high X-ray doses.[14] The sparing consequence of microbeams in customary tissues is an amalgamation of two phenomena, that is the biological repair effect and volume effect. The biological repair effect in usual tissue sparing is mediated in part by the tissue's microvasculature that regenerates actually from the angiogenic cells surviving between the beams.[14] While the volume effect refers to the principle that the threshold dose for radiation damage to the tissue increases as the volume of the irradiated tissue decreases.[14–16] So it was found that peak and valley irradiated zones were not distinguishable in tumors within 24 h of MRT probably due to a coordinated restore response.[17]

Another radiobiological problem has to be addressed for MRT is radiation-induced bystander effects (RIBEs) and RIBEs is defined as the frequency of biological effects in non-irradiated cells resulting from exposure of other cells to radiation.[18] Bystander cells in exposed cell populations can be illustrated as the non-irradiated cells that obtained signals from neighboring or distant irradiated cells. While the molecular radiobiological mechanism still is under exploration. There were a few reports concerning the function of RIBEs in MRT, RIBEs in non-target normal cells similar to human fibroblasts could be observed after MRT.[11] However, it is early to conclude that RIBEs might be a source of extra stress for normal tissues during MRT therapy. As the impact of RIBEs is anticipated to lessen gradually as much as the distance from the targeted cells increases[19] but it ain't completely understood that RIBEs may be one of the reason for the necrosis and hypervascularity phenomenon observed in the area close to the tumor during MRT treatments.[20]

Sharma et al.[21] were observed that nearly identical absorbance prototypes in protein and lipid regions MRT peak and valley regions showed a holistic tissue response to MRT and chemical shifts corresponding to the nucleic acid region between the peak and valley dose regions.[21] It can be the first evidence for a mechanism by which MRT kills the whole tumor despite only a small percentage receiving peak irradiation. In additional study, compared to broad beam, expression of a number of genes, including major histocompatibility complex (MHC) class II antigen gene family members, and other immunity-related genes including Ciita, Ifng, Cxcl1, Cxcl9, Indo and Ubd changes in *in vivo* MRT and the findings revealed molecular disparities in the tumor response to microbeam versus broad beam irradiation.[22]

Photon activation therapy (PAT): physical aspects

PAT is a two-step system. In the first step, tumor cells loaded with high *Z* atoms like contrasting agents i.e. iodinated compounds and platinum-containing drugs. While the second step involves, high *Z*

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atoms such as In, Pt, Au, I or Br interaction with electromagnetic radiations and enhance the radiation dose to a cancerous tumor, but do not harm the surrounding normal tissue cells. The use of X-ray energies in the tens of keV range rather than MV, X-ray is essential for the success of this treatment due to the prevalence of the photoelectric effect at these energies.[23] During treatments, a large number of secondary electron particles such as Auger and photoelectrons are grouped in the tumor when the irradiation acts together with high *Z* atoms via a photoelectric effect. Per se, the secondary electrons deposit their energy near the atom where photo-absorption takes place and produce lethal damage to the tumor cells.[24] Hence, the SR with a tunable, keV energy can obliterate the tumor cells in a selective way.

Biological aspects of PAT

There is probability synergistic interaction between the high-*Z* containing chemotherapeutic agents and SR, and it laid an opinion on the applicability of PAT in the clinical uses. Initially, the high-Z containing chemotherapeutic agents such as platinum-containing drugs i.e. cisplatin, carboplatin, and oxaliplatin etc. kill tumor cells via the stimulation of slowly repairable DNA double-strand breaks, and inhibition of DNA-protein kinase activity, resulting in remarkable nuclear relocalization of RAD51, hyperphosphorylation of the BRCA1 protein, and activation of proto-oncogenic like c-Abl tyrosine kinase.[24] Besides, ionized molecules by SR may cause breaking of chemical bonds, disruption of the structural arrangement of macromolecules, for instance, DNA and result in severe consequences if not repaired effectively or in time. Moreover, because of the high-*Z* agents like platinum can be specifically photoactivated by SR at the *K*-edge of the agent. For example, 78.4 keV corresponds to the *K*-edge of platinum, X-ray energy induced by SR is higher (about 80keV) through the photoactivation of platinum, Auger electrons are created through photoelectric effect and about 95% of these Auger electrons have energies below 3 keV but lead to a high linear energy transfer (LET) and would thus be responsible for greater biological effectiveness.[25] Therefore, these rationales can support a new advancement in cancer diagnosis and treatment concurrently.

Stereotactic synchrotron radiation therapy (SSRT): physical characteristics

Many preclinical studies have been done and are also ongoing using monochromatic X-rays at the ESRF biomedical beam-line. Similar to PAT technique, SSRT is a new treatment for the cancerous tumors and it is based on the production of photo-activation. Two different approaches have been simultaneously applied for SSRT. The first approach is contrast-enhanced synchrotron radiation therapy, with some extracellular agents like iodine. The second approach uses chemotherapeutic drugs containing platinum or iodine compounds. The advances of new in vitro experiments using these new metallic compounds are necessary and in some cases are associated with liposomes or other delivery systems. The SSRT technique involves in targeting tumors loaded with high-*Z* elements, stereotactic irradiation would be delivered with the medium energy X-ray and the dose has to be geometrically restricted to the tumor size only but does not harm to normal tissue cells. Furthermore, synchrotron source also supplies the tunable and strong monochromatic beams. So, higher fraction dose could be delivered to the target side within a shorter time compared to conventional radiotherapy. The tolerances of motions of the tumor are well within the limits. Since target movement during irradiation consequently results in the missing of the treated tumor, the therapeutic effect is much enhanced by the local deposition of energy and hypofractionated irradiation by SSRT. New-generation gold nanoparticles can also cause apoptotic damage in tumor cells and have a significant role in enhancing both chemotherapy drug concentration as well as radiation dose inside the radio-resistant tumors, while no harmful effect to healthy tissues. The use of some lipid-based vehicles like liposomes can further improve drug delivery within the tumor. To date, approximately all the preclinical studies involving synchrotron X-ray radiation have been performed on rats.

Biological characteristics of SSRT

Radiation therapy is generally delivered at low doses of irradiation (1.5−3Gy) that are administered daily over weeks. The stereotactic radiation therapy (SRT) delivers higher single biological equivalent dose that is greater than 5Gy per fraction within shorter period compared to conventional RT. The PAT-based SSRT could have both radiobiological benefits of PAT and SRT. Since higher energy within one dose fraction is delivered by SSRT compared to RT and SRT, it could have some difference from RT in terms of the actual mechanism of tumor killing. The acid sphingomyelinase (ASMase) pathway has been implicated in the rapid endothelial apoptosis, followed by the death of cells that appeared to be intact for 2−3 days after a single high dose of irradiation.[26] This mechanism of tumor killing was not observed in mice treated with conventionally fractionated RT. While some studies have proved that a higher fractionated dose of irradiation i.e. SSRT technique could more proficiently initiate the apoptosis of cancer stem cells than conventional RT.[27] Furthermore, tumor response to hypofractionated irradiation can be related to the regulation of $CD8^+$ T cells. In Lee's study, the delivery of 15−25Gy dose per fraction was found to cause a significant increase in T cell priming in draining lymphoid tissue, leading to reduction or eradication of the primary tumor or distant metastasis in a $CD8^+$ T cell-dependent fashion in an animal model.[28] Therefore, synchrotron-based PAT and stereotactic radiotherapy present a promising way of radiotherapy to kill cancer.

Applications of different radiotherapy techniques

Applications of MRT

MRT in small animals: Preclinical long-term studies that were conducted on different species such as insects, birds, rodents, and pigs have revealed an amazing tolerance of normal organs and blood vessels exposed to fractionated radiation doses in excess of 100Gy delivered by arrays of microbeam (MB).[29,30] This tolerance was particularly obvious in suckling rats and weaning piglets, whose irradiated brains were still developing.[29,31] MRT in small animal models has achieved therapeutic ratios that evidently surpass those achieved by conventional radiography with a homogeneous dose distribution, in a range of malignancies, including gliomas, gliosarcomas, glioblastomas and human squamous cell carcinomas.[29]

This led to the need of using MRT jointly with radiation-enhancing substances or cytostatic drugs. In the presence of high-*Z* elements, such as gadolinium, gold, thallium, and lutetium, acted as a dose enhancer, it can maximize of the ratio between the peak and valley dose ratio (PVDR) values in healthy tissue respect to the PVDR in the tumor and minimize of bone and brain valley doses.[32,33] These attributes of MRT have been extensively demonstrated by results of preclinical experiments.[34,35] Moreover, MRT-related bystander effects have also been recognized.[26–38] The tumor control of MRT has been

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improved by combining MRT with various compounds,[29] gene-mediated immunoprophylaxis,[39] radiation enhancing substances,[40] and other adjuvant techniques.

It could clearly be concluded that high-dose, high-precision radiotherapies with a decreased possibility of normal tissue problems offer a prediction of improved survival result probability and cut the risk of therapy-related toxicity. Various possible reasons why MRT offers a higher therapeutic index for tumors than broad beam irradiation have been explained as the following- (a) MBs generate steep dose gradients between tissue slices getting the peak and valley doses; they have a 90%-10% dose fall-off, about 200 times steeper than that of a Gamma Knife.[29] The radiotoxic dose hence remains in a very narrow zone however the functionality and integrity of the adjoining normal tissue in the valleys between the peaks could be preserved. (b) Spatial fractionation results in a very large specific contact surface between peak and valley zones and this lengthen contact surface is for the repair of heavily irradiated tissues in peak regions. (c) on the contrary to the high tolerance of the normal arteries[41] and microvasculature[42] to irradiation by MB, the tumor vasculature of 9L gliosarcomas in rats is selectively damaged by MRT[43] with resulting tumor shrinkage and hypoxia. On the other hand, normal brain tissues exposed to MB during MRT stay adequately perfuse to preserve normoxia.[35] (d) Probable antioncogenic apoptotic proteomic alteration indicates that the combined interaction of such MB irradiation-induced bystander effect proteins might give a protective effect on normal tissues.[37]

MRT for large animals: The preceding preclinical results in small animals are not adequate to validate MRT studies to go forward directly to phase-I human clinical trials. Prior to moving to human applications, MRT should be applied in therapeutic veterinary trials of larger animals such as pigs bearing intra-cerebral glial tumors as well as companion cat and dog patients having spontaneous tumors.[29,44] The MRT studies on larger animals are supported by the physiological and dimensional similarities of spontaneous tumors in dogs and cats compared to those in human malignancies, in contrast to implanted tumors of mice and rats.[45–48] These studies will further enhance our perceptive of how larger and deeper-seated tumor tissues respond to MRT and provide as an early warning system for unpredicted late adverse effects.

MRT for human patients: MRT for human patients requires a careful, multi-disciplinary evaluation of epidemiological, logistical, medical, and ethical considerations, including quality of life in contrast to lifespan, and endpoint definitions. Current standard treatment consists of surgery followed by chemoradiation and adjuvant temozolomide but no standard of care exists for patients with recurrent tumors.[49] The pediatric patients with diffuse intrinsic pontine glioma (DIPG) can be an excellent candidate population.[29] DIPG remains a most annoying tumor in pediatric oncology. Due to the location of tumors and the complexity in characterizing tumor tissue from normal structures, surgical debulking is inhibited by the considerable threat of mortality and morbidity. The basis of remedy for intrinsic pontine glioma has been RT. While there are facts that conventional RT offers short-term advantages, long-term results have been miserable and the overall survival time has not changed.[50,51] To safely conduct human clinical trials with MRT, new hardware and software need to be developed and tested. A patient positioning system for MRT is currently available for small animals and larger animals such as pigs, dogs, and cats, up to a weight of 40 kg. Designing and building a patient-positioning system that will move a heavier human patient with the required exactness/ spatial precision are therefore necessary. The therapy accuracy system used in the large animal trials was based on computed tomographic images. For clinical trials in humans, therapy planning which incorporates magnetic resonance imaging findings is desirable, as it provides higher spatial resolution.[52]

For imminent clinical trials, protected irradiation protocols in microbeam radiation therapy were defined by means of Monte Carlo simulations. In this, a unidirectional irradiation with a field size of $2\times2cm^2$ and a centrally located tumor, the largest peak and valley doses attainable in the tumor are 55Gy and 2.6Gy, respectively. The consequent maximum valley doses received by the skin, healthy brain and bone were 4Gy, 7Gy and 14Gy (doses in one fraction), respectively.[53] Emergent experimental confirmation is showing that MRT could be a new move toward the treatment of cancer. The submillimetric beams could be transported following a stereotactic design conveying to the target doses in the value of hundreds of Gray with no harm to the neighboring tissues, which means MRT can combine with SSRT. Microbeam arrays can also be used to produce cortical transections or subcortical lesions, therefore enabling the non-invasive intonation of brain networks. MRT is also of great interest for the treatment of a variety of brain disorders, including functional diseases like movement disorders and epilepsy.[54]

Application of PAT

The high-*Z* containing compounds like iodinated contrast agents, platinum-containing drugs, for instance, cisplatin, carboplatin and oxaliplatin, and nanoparticles have been studied in both *in vitro* and *in vivo*.[55,56] In the early 80's, Norman's group proposed to treat brain tumors, after administering patients with an iodinated contrast agent and computed tomography (CT) scanners were used as therapy machines to enhance the local dose deposition.[57] The result of the phase-I clinical trial about PAT was firstly reported in 1999,[58] the study was designed to assess CT scanner as a tool for radiation therapy of human brain tumors. The experiment was conducted on eight patients with a small metastatic brain tumor received 3−5 weekly fractions of 5Gy equivalent doses from a modified CT scanner to deliver radiation therapy. Most of the patients also received conventional 40Gy before, during, or after PAT. The tumor treated by PAT in two patients' attained complete response, when compared with the control tumor in patients (which had not treated by PAT). Monte Carlo calculations of the radiation dose distributions in a model tumor demonstrated that the PAT irradiation of tumors carrying 10 mg or more of iodine per gram of tumor was as good or better than the dose distribution from conventional 10-MV X-ray. The author concluded PAT could be very useful in the control of iodinated X-ray contrast media enhanced and other small brain tumors. Hence, the future of PAT in clinical application is promising in China due to the availability of SSRF.

Applications of SSRT

Some animal experiments turned out that high *Z* elements such as iodinated contrast agent, heavy elements (i.e. gold nanoparticles) and platinum-based chemotherapy can lead to dose enhancement and long survival time in high-grade glioma in a combination of high fractionation of radiation.[59–61] Based on those optimistic results of pre-clinical studies, SSRT may have the probability of curing radiation refractory brain tumors, such as high-grade gliomas. A phase I clinical trial has been suggested to assess the safety and possible therapeutic effectiveness of convection-enhanced delivery of carboplatin in patients with recurring glioblastomas, and ultimately a phase II trial

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of carboplatin in grouping with radiation therapy, dose comparison showed that SSRT can give enhanced results than other techniques providing *Iodine*>2 mg·mL^{-1}.[62] Prior to SSRT is executed into the clinic, the necessities for radiation dose monitoring, safety systems, fast shutters, and patient positioning stage have to be fulfilled. The handling protocol at ESRF has considered the following issues.[63] Initially, the location and size of the tumor are defined by X-ray CT and MRI, while X-ray SR-CT imaging at the ESRF is also necessary for correct positioning of the patient following the treatment planning. Afterwards, a support needed for a precise transfer of the tumor coordinates. Then, the patient is translated and/or rotated with great precision during the treatment, and the radiation dose is monitored. Any deviation from the prescribed doses and treatment protocol will trigger closing of fast shutters and/or trip the storage ring. The doses received by the tumor and healthy tissues were calculated by using Monte Carlo simulations (PENELOPE code) to estimate the possible risks. With the dose enhancement factors determined in different situations, a scheme for the dose escalation in the various phases of the clinical trials has been proposed.[64]

Conclusion

The development of innovative facilities of synchrotron radiation in the world is increasing rapidly. Synchrotron radiation has demonstrated to have a number of advantages in terms of physical and biological features. This shows possibilities to be applied in the treatment of various types of cancer. Radio-resistant cancer like gliomas and untreatable brain tumor of children could be the targets of SSRT, MRT or PAT can be used for the management of tumors like lung cancer, liver cancer etc. within a short time of duration. Because the tumor frequently moves during fractionated irradiation owing to respiration movement. Along with the SR-based radiotherapy clinical trials carried out around the world, synchrotron radiation would produce as an outstanding radiation source which may motivate the researchers towards the development of inimitable treatment of cancers clinically for settings of today.

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Conflict of interest

Author's have no conflict of interest in the content of this review article.

References

1. Curtis HJ. The use of deuteron microbeam for simulating the biological effects of heavy cosmic-ray particles. *Radiat Res Suppl*. 1967;7:250−257.
2. Suortti P, Thomlinson W. Medical applications of synchrotron radiation. *Phys Med Biol*. 2003;48(13):1–35.
3. Arfelli F, Assante M, Bonvicini V, et al. Low-dose phase contrast x-ray medical imaging. *Phys Med Biol*. 1998;43:2845–2852.
4. Bravin A, Fiedler S, Thomlinson W. Proc SPIE. 2002;4682:167.
5. Adam JF, Biston MC, Joubert A, et al. Enhanced delivery of iodine for synchrotron stereotactic radiotherapy by means of intracarotid injection and blood–brain barrier disruption: Quantitative iodine biodistribution studies and associated dosimetry. *Int J Radiat Oncol Biol Phys*. 2005;61(4):1173–1182.
6. Rousseau J, Boudou C, Barth RF, et al. Enhanced Survival and Cure of F98 Glioma–Bearing Rats following Intracerebral Delivery of Carboplatin in Combination with Photon Irradiation. *Clin Cancer Res*. 2007;13(17):5195–5201.
7. Adam JF, Joubert A, Biston MC, et al. Prolonged survival of Fischer rats bearing F98 glioma after iodine-enhanced synchrotron stereotactic radiotherapy. *Int J Radiat Oncol Biol Phys*. 2006;64(2):603–611.
8. Behin A, Hoang-Xuan K, Carpentier AF, et al. Primary brain tumours in adults. *Lancet*. 2003;361(9354):323–331.
9. Anschel DJ, Bravin A, Romanelli P. Microbeam radiosurgery using synchrotron-generated submillimetric beams: a new tool for the treatment of brain disorders. *Neurosurgical Review*. 2011;34(2):133–142.
10. Deman P, Edouard M, Besse S, et al. Radiothérapie par rayonnement synchrotronSynchroton radiotherapy. La Revue de Médecine Interne. 2010;31(8):586–589.
11. Régnard P, Bräuer-Krisch E, Troprès I, et al. Enhancement of survival of 9L gliosarcoma bearing rats following intracerebral delivery of drugs in combination with microbeam radiation therapy. European Journal of Radiology. 2008;68(3):S151−155.
12. Siegbahn EA, Stepanek J, Bräuer-Krisch E. Determination of dosimetrical quantities used in microbeam radiation therapy (MRT) with Monte Carlo simulations. *Medical Physics*. 2006;33:3248−3259.
13. Crosbie JC, Svalbe I, Midgley SM. A method of dosimetry for synchrotron microbeam radiation therapy using radiochromic films of different sensitivity. *Phys Med Biol*. 2008;53:6861−6877.
14. Bräuer-Krisch E, Serduc R, Siegbahn EA. Effects of pulsed, spatially fractionated, microscopic synchrotron X-ray beams on normal and tumoral brain tissue. *Mutat Res*. 2010;704(1–3):160−166.
15. Serduc R, Bräuer-Krisch E, Siegbahn EA. High-Precision Radiosurgical Dose Delivery by Interlaced Microbeam Arrays of High-Flux Low-Energy Synchrotron X-Rays. *PLoS One*. 2010;5:e9028.
16. Stone HB, Coleman CN, Anscher M S. Effects of radiation on normal tissue: consequences and mechanisms. *Lancet Oncology*. 2003;4(9):529−536.
17. Crosbie JC, Anderson RL, Rothkamm K. Tumor Cell Response to Synchrotron Microbeam Radiation Therapy Differs Markedly From Cells in Normal Tissues. *Int J Radiat Oncol Biol Phys*. 2010;77(3):886−894.
18. Prise KM, O'Sullivan JM. Radiation-induced bystander signalling in cancer therapy. *Nat Rev Cancer*. 2009;9:351−360.
19. Hamada N, Matsumoto H, Hara T. Intercellular and Intracellular Signaling Pathways Mediating Ionizing Radiation-Induced Bystander Effects. *J Radiat Res*. 2007;48(2):87−95.
20. Sprung CN, Cholewa M, Usami N. DNA damage and repair kinetics after microbeam radiation therapy emulation in living cells using monoenergetic synchrotron X-ray microbeams. *J Synchrotron Radiat*. 2011;18(4):630−636.
21. Sharma M, Crosbie JC, Puskar L, et al. Microbeam-irradiated tumour tissue possesses a different infrared absorbance profile compared to broad beam and sham-irradiated tissue. *Int J Radiat Biol*. 2013;89(1):79−87.
22. Sprung CN, Yang Y, Forrester HB. Genome-wide transcription responses to synchrotron microbeam radiotherapy. *Radiat Res*. 2012;178(4): 249−259.
23. Robar JL, Riccio SA, Martin MA. Tumour dose enhancement using modified megavoltage photon beams and contrast media. *Phys Med Biol*. 2002;47:2433−2449.
24. Corde S, Balosso J, Elleaume H. Synchrotron Photoactivation of Cisplatin Elicits an Extra Number of DNA Breaks That Stimulate RAD51-mediated Repair Pathways. *Cancer Res*. 2003;63:3221−3227

25. Karnas SJ, Yu E, McGarry RC. Optimal photon energies for IUdR K-edge radiosensitization with filtered x-ray and radioisotope sources. *Phys Med Biol*. 1999;44:2537−2549.

26. Garcia-Barros M, Paris F, Cordon-Cardo C. *Science*. 2003;300:1155−1159.

27. Balcer-Kubiczek EK. Apoptosis in radiation therapy: a double-edged sword. *Exp Oncol*. 2012;34(3):277−285.

28. Lee Y, Auh SL,Wang Y. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood*. 2009;114(3):589−595.

29. Grotzer MA, E Schültke, E Bräuer-Krisch, et al. Microbeam radiation therapy: Clinical perspectives. *Physica Medica*. 2015;31(6):564−567.

30. Bencokova Z, Balosso J, Foray N. Radiobiological features of the anti-cancer strategies involving synchrotron X-rays. *J Synchrotron Radiat*. 2008;15:74−85.

31. Hanson AL, Slatkin DN, Laissue J. Unidirectional X-ray microbeam radiosurgery of infantile neuraxial malignancies: estimations of tolerable valley doses. Proc SPIE. 2013: 8565.

32. Prezado Y, Fois G, Le Duc G. Gadolinium dose enhancement studies in microbeam radiation therapy. *Med Phys*. 2009;36(8):3568−3574.

33. Martínez-Rovira I, Prezadoa Y. Monte Carlo dose enhancement studies in microbeam radiation therapy. *Med Phys*. 2011;38(7):4430−4439.

34. Bouchet A, Bidart M, Miladi I, et al. Characterization of the 9L gliosarcoma implanted in the Fischer rat: an orthotopic model for a grade IV brain tumor. *Tumour Biol*. 2014;35(7):6221−6233.

35. Bouchet A, Lemasson B, Christen T, et al. Synchrotron microbeam radiation therapy induces hypoxia in intracerebral gliosarcoma but not in the normal brain. *Radiother Oncol*. 2013;108(1):143−148.

36. Fernandez-Palomo C, Schultke E, Smith R, et al. Bystander effects in tumor-free and tumor-bearing rat brains following irradiation by synchrotron X-rays. *Int J Radiat Biol.* 2013;89(6):445−453.

37. Smith RW, Wang J, Schultke E, et al. Proteomic changes in the rat brain induced by homogenous irradiation and by the bystander effect resulting from high energy synchrotron X-ray microbeams. *Int J Radiat Biol*. 2013;89(2):118−127.

38. Mothersill C, Fernandez-Palomo C, Fazzari J, et al. Transmission of signals from rats receiving high doses of microbeam radiation to cage mates: an inter-mammal bystander effect. *Dose Response*. 2014;12(1):72e92.

39. Smilowitz HM, Blattmann H, Brauer-Krisch E, et al. Synergy of gene-mediated immunoprophylaxis and microbeam radiation therapy for advanced intracerebral rat 9L gliosarcomas. *J Neurooncol*. 2006;78(2):135−143.

40. Le Duc G, Miladi I, Alric C, et al. Toward an image-guided microbeam radiation therapy using gadolinium-based nanoparticles. *ACS Nano*. 2011;5(12):9566−9574.

41. van der Sanden B, Brauer-Krisch E, Siegbahn EA, et al. Tolerance of arteries to microplanar X-ray beams. *Int J Radiat Oncol Biol Phys*. 2010;77(5):1545−1552.

42. Serduc R, Verant P, Vial JC, et al. *In vivo* two-photon microscopy study of short-term effects of microbeam irradiation on normal mouse brain microvasculature. *Int J Radiat Oncol Biol Phys*. 2006;64(5):1519−1527.

43. Bouchet A, Lemasson B, Le Duc G, et al. Preferential effect of synchrotron microbeam radiation therapy on intracerebral 9L gliosarcomas vascular networks. *Int J Radiat Oncol Biol Phys*. 2010;78(5):1503−1512.

44. Selek L, Seigneuret E, Nugue G, et al. Imaging and histological characterization of a human brain xenograft in pig: the first induced glioma model in a large animal. *J Neurosci Methods*. 2014;221:159−165.

45. Lindblad-Toh K, Wade CM, Mikkelsen TS, et al. Genome sequence, comparative analysis and haplotype structure of the domestic dog. *Nature*. 2005;438(7069):803–819.

46. Khanna C, Lindblad-Toh K, Vail D, et al. The dog as a cancer model. *Nat Biotechnol*. 2006;24(9):1065–1066.

47. Vail DM. Cancer clinical trials: development and implementation. *Vet Clin North Am Small Anim Pract*. 2007;37(6):1033−1057.

48. MacEwen EG. Spontaneous tumors in dogs and cats: models for the study of cancer biology and treatment. *Cancer Metastasis Rev* 1990;9(2):125−136.

49. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987−996.

50. Khatua S, Moore KR, Vats TS, et al. Diffuse intrinsic pontine gliomacurrent status and future strategies. *Childs Nerv Syst*. 2011;27(9):1391−1397.

51. Jansen MH, Veldhuijzen van Zanten SE, Sanchez Aliaga E, et al. Survival prediction model of children with diffuse intrinsic pontine glioma based on clinical and radiological criteria. *Neuro Oncol*. 2015;17(1):160–166.

52. Uh J, Merchant TE, Li Y, et al. MRI-based treatment planning with pseudo CT generated through atlas registration. *Med Phys*. 2014;41(5):051711.

53. Martínez-Rovira I, Sempau J, Fernández-Varea JM. Monte Carlo dosimetry for forthcoming clinical trials in x-ray microbeam radiation therapy. *Phys Med Biol*. 2010;55:4375−4388.

54. Romanelli P, Bravin A. Synchrotron-generated microbeam radiosurgery: a novel experimental approach to modulate brain function. *Neurol Res*. 2011;33:825−831.

55. Tange Y, Miyazaki M, Iwata J. Novel antitumor effect of carboplatin delivered by intracerebral microinfusion in a rat malignant glioma model. *Neurol Med Chir*. 2009;49(12):572−579.

56. Gastaldo J, Bencokova Z, Massart C. Specific molecular and cellular events induced by irradiated X-ray photoactivatable drugs raise the problem of co-toxicities: particular consequences for anti-cancer synchrotron therapy. *J Synchrotron Radiat*. 2011;18:456−463.

57. Santos Mello R, Callisen H, Winter J. Radiation dose enhancement in tumors with iodine. *Med Phys*. 1983;10(1):75−78.

58. Rose J H, Norman A, Ingram M. First radiotherapy of human metastatic brain tumors delivered by a computerized tomography scanner (CTRx). *Int J Radiat Oncol Biol Phys*. 1999;45(5):1127−1132.

59. Adam JF, Biston MC, Rousseau J. Heavy element enhanced synchrotron stereotactic radiotherapy as a promising brain tumour treatment. *Phys Med*. 2008;24(2):92−97.

60. Edouard M, Broggio D, Prezado Y. Treatment plans optimization for contrast-enhanced synchrotron stereotactic radiotherapy. *Med Phys*. 2010;37(6):2445−2456.

61. Rousseau J, Boudou C, Barth R F. Enhanced Survival and Cure of F98 Glioma–Bearing Rats following Intracerebral Delivery of Carboplatin in Combination with Photon Irradiation. *Clin Cancer Res*. 2007;13:5195−5201.

62. Yang W, Huo T, Barth R F. Convection enhanced delivery of carboplatin in combination with radiotherapy for the treatment of brain tumors. *J Neurooncol*. 2011;101:379−390.

63. Renier M, Brochard T, Nemoz C. The radiotherapy clinical trials projects at the ESRF: Technical aspects. *Eur J Radiol*. 2008;68(3):S147−150.

64. Prezado Y, Fois G, Edouard M. Biological equivalent dose studies for dose escalation in the stereotactic synchrotron radiation therapy clinical trials. *Med Phys*. 2009;36(3):725−733.

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