Potential applications of synchrotron radiation to the treatment of cancer

SHI Zeliang[1] ZHOU Shuhui[2] FU Shen[1,*]

[1]*Department of Radiation Oncology, Shanghai No.6 People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai 200233, China*

[2]*Medical College of Soochow University Radiology and Protection Institute, Suzhou 215123, China*

Abstract Although conventional radiotherapy remains to be one of the most useful treatments for cancer, it is not the best strategy to maximize the effects on the tumors and minimize the damage to the surrounding tissues due to its physical and biological characteristics. Synchrotron radiation (SR) with uniquely physical and biological advantages may represent an innovative approach for cancer treatment. In recent years, SR-based photon activation therapy, stereotactic synchrotron radiation therapy and micro-beam radiation treatment have been developed, and the results of *in vitro* and *in vivo* experiments are very promising. It is necessary to understand the physical and radiobiological principle of those novel strategies before the approach is applied to the clinic. In this paper, we summarize the advances of SR in terms of physical, radiobiological advantages and its potential clinical applications. With the successful operation of shanghai synchrotron radiation, good opportunities in China have been provided for investigations on the treatment of cancer with synchrotron radiation.

Key words Synchrotron radiation, Photon activation therapy, Stereotactic synchrotron radiation therapy, Microbeam radiation therapy

1 Introduction

Surgery, chemotherapy and radiotherapy are the well-established modalities for cancer treatment. Since Wilhelm Conrad Röntgen's discovery of X-ray in 1895[1], X-ray has been widely used in medical diagnosis and cancer treatment[2]. The radiotherapy has been rapidly adapted into the treatment of cancer and plays a critical role in 60−70% of cancer patient treatment. The existing technique of radiotherapy, such as conventional MV X-ray radiation therapy, still has limitations in terms of physical and radiobiological aspects. Therefore, it is imperative to develop new technology to maximize the dose to a tumor while minimizing radiation damage to the surrounding normal tissues. The advent of synchrotron radiation (SR) has opened a new option to the radiotherapy. Shanghai Synchrotron Radiation Facility (SSRF), a third-generation of synchrotron radiation light source commissioned in 2009, would be an invaluable tool for cancer treatment.

2 Shanghai synchrotron radiation facility

Shanghai Synchrotron Radiation Facility (SSRF), a 3.5-GeV 3rd generation facility, was ground broken in 2004 and commissioned in 2009. Its performance is optimized for high brightness X-ray radiation up to 100 keV, which is about 10^{10} times brighter than that of conventional X-tube. The light flux is more than 10^{15} photons/(s.0.1%bw). The high flux density leads to the possibility to develop new methods for radiation therapy and reduce greatly the data collecting time. Especially it has very high stability, which can supply stable beam for many hours. The beam position stability is about 10% of the spot size. SSRF can operate at different modes according to the researchers' demands, so that it can satisfy the requirements from different users.

Supported by Shanghai Jiaotong University and Science and Technology Commission of Shanghai, China (Nos. YG2012ZD02 and 12JC1407400) and National Natural Science Foundation of China (Nos.81272506 and 61227017)

* Corresponding author. *E-mail address:* Shen_fu@hotmail.com

Received date: 2012-11-27

3 Potential applications in the preclinical and clinical application

3.1 Photon activation therapy (PAT)

3.1.1 Physical aspects of PAT

Photon Activation Therapy (PAT) is a two-step system, tumor cells loaded with high *Z* atoms (such as iodinated contrast agents and platinum-containing drugs) , high *Z* atoms will interact with electromagnetic radiations and increase the radiation dose to a cancerous tumor, while sparing the surrounding normal tissues. 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[3]. A larger number of secondary particles like Auger and photoelectrons are gathered in the tumor when the irradiation interacts with high *Z* atoms through a photoelectric effect. The extra energy that the secondary particle cascade delivers to the cell can be tens of keV. As such, the secondary electrons deposit their energy near the atom where photoabsorption takes place and produce lethal damage to the tumor cells[4]. Therefore, SR with a tunable, keV energy could destroy the tumor cells in a selective way.

3.1.2 Biological aspects of PAT

There were possible synergistical interaction between SR and the high-Z containing chemotherapeutic agents and it lay a ground for the application of PAT in the clinic.

Firstly, the high-Z containing chemotherapeutic agents like platinum-containing drugs (cisplatin, carboplatin and oxaliplatin) kill tumor cells through the induction of slowly repairable DNA double-strand breaks, inhibition of DNA-protein kinase activity, resulting in dramatic nuclear relocalization of RAD51, hyperphosphorylation of the BRCA1 protein, and activation of proto-oncogenic like c-Abl tyrosine kinase[4]. In addition, ionized molecules by SR, which are highly reactive, can cause breaking of chemical bonds, disrupts the structure of macromolecules, such as DNA and result in severe consequences if not repaired adequately or in time. Furthermore, since the high-*Z* agents like platinum could 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 80 keV) 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[5]. Therefore, those rationals may promote a new approach for cancer diagnosis and treatment at the same time.

3.1.3 Application of PAT in the preclinical and clinical setting

The high-*Z* containing compound like iodinated contrast agents, platinum-containing drugs (cisplatin, carboplatin and oxaliplatin) and nanoparticles have been studied in both *in vitro* and *in vivo*[6,7].

In the early 80's, Norman's group proposed to treat brain tumors, after loading patients with iodinated contrast agents, computed tomography (CT) scanners served as therapy machines to enhance the local dose deposition[8]. The outcome of phase I clinical trial about PAT was firstly reported in 1999[9], the study was designed to evaluate CT scanner as a device for radiation therapy of human brain tumors. 8 patients with a small metastatic brain tumor received 3−5 weekly fractions of 5 Gy equivalent doses from a CT scanner that was modified to deliver radiation therapy. Most of patients also received conventional 40 Gy before, during, or after PAT. The results showed that the treatment was well tolerated. The tumor treated by PAT in two patients achieved complete response, whereas the control tumor in those patients, which had not covered by PAT, only had stable disease. Monte Carlo calculations of the radiation dose distributions in a model tumor showed 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. Therefore, the future of PAT in clinical application is promising in China due to the availability of SSRF.

3.2 Stereotactic synchrotron radiation therapy (SSRT)

3.2.1 Physical aspects of SSRT

Similar to PAT, SSRT is a new treatment based on the production of photoactivation. SSRT involves in targeting tumors loaded with high-*Z* elements, stereotactic irradiation will be delivered with the medium energy X-ray and the dose has to be geometrically restricted to the tumor size. In addition, synchrotron source can provide the tunable and intense monochromatic beams. Therefore, higher fraction dose can be delivered to the target within shorter time compared to conventional radiotherapy. The tolerances of motions of tumor are well within the limits. Since target movement during irradiation consequently result into the missing of the treated tumor, the therapeutic effect is much enhanced by the local deposition of energy and hypofractionated irradiation by SSRT.

3.2.2 Biological aspects of SSRT

RT is usually delivered at low doses (1.5−3 Gy) that are administered daily over weeks, steotactic radiation therapy (SRT) is defined as higher single dose (>5 Gy) per fraction, biological equivalent total dose is given within shorter period by SRT compared to conventional RT, PAT-based SSRT may have both radiobiological advantages of PAT and SRT. Since higher energy within one dose fraction is given by SSRT compared to RT and SRT, it may have some difference from RT in terms of the actual mechanism of tumor killing. Firstly, the acid sphingomyelinase (ASMase) pathway has been implicated in the rapid endothelial apoptosis, followed by death of cells that appeared to be intact for 2−3 days after a single high dose of irradiation[10]. This mechanism of tumor killing was not observed in mice treated with conventionally fractionated RT. Secondly, some studies have proved that a higher fractionated dose of irradiation could more efficiently initiate the apoptosis of cancer stem cells than conventional RT[11]. Furthmore, tumor response to hypofractionated irradiation may be related to the regulation of CD8+ T cells. In Lee's study, the delivery of 15−25 Gy 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[12]. Therefore, synchrotron-based PAT and stereostatic radiotherapy present a promising way of radiotherapy to kill cancer.

3.2.3 Application of SSRT in the preclinical and clinical setting

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 combination of high fractionation of radiation[13-15]. Based on those promising results of preclinical studies, SSRT may have the capability of curing radiation refractory brain tumors, such as high-grade gliomas.

A phase I clinical trial has been proposed to evaluate the safety and potential therapeutic efficacy of convection-enhanced delivery of carboplatin in patients with recurrent glioblastomas, and ultimately a phase II trial of carboplatin in combination with radiation therapy, dose comparison showed that SSRT could give better results than any other techniques providing $[I]>2$ mg·mL^{-1}[16]. Before SSRT is implemented into the clinic, the requirements for radiation dose monitoring, fast shutters, safety systems, and patient positioning stage have to be satisfied. The treatment protocol at ESRF have considered the following issues[17]. Firstly, 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 correctly positioning the patient following the treatment planning. Second, a support needed for an accurate transfer of the tumor coordinates. Third, 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[18].

3.3 Microbeam radiation therapy (MRT)

3.3.1 Physical aspects of MRT

Microbeam radiation therapy (MRT) is a technique using highly collimated, quasi-parallel co-planar or cross-planar arrays of highly intense microbeams produced by synchrotron. The production of such microbeams, which is typically between 25 and 100 μm full width at half maximum (FWHM) values and 100-400 μm center-to-center (c-t-c) spacing, requires a multi-slit collimator either with fixed or adjustable microbeam width. The minimum dose in the central region between two microbeams is called the "valley dose.", the highest dose level called as "peak dose" is in the overlap area of microbeams, the peak and valley dose ratio (PVDR) in the irradiation field are believed to be of importance for the therapeutic effect of the treatment and strongly depends on the varieties of parameters such as X-ray spectrum, sample size and composition, irradiation field and depth, the distance between peaks, etc. The PVDR is a critical parameter that has to be optimized in MRT[19-21]. 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.

3.3.2 Biological aspects of MRT

MRT irradiation is generally based on a single fraction of radiation dose delivered either unidirectionally or bidirectionally (co- or cross-planar) and shares the similar advantage as SSRT in terms of radiobiological effect of hypofractionated irradiation. In addition, peak entrance doses of several hundreds of grays are surprisingly well tolerated by normal tissues. Experiments have been performed on different animal models, including mice, rats, duck embryos, piglets and rabbits. The results have shown that a particular resistance of normal tissues to high X-ray doses[22]. The sparing effect of microbeams in normal tissues is a combination of two phenomena: the volume effect and the biological repair effect. 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[22-24], and the biological repair effect in normal tissue sparing is mediated in part by the tissue's microvasculature that regenerate apparently from the angiogenic cells surviving between the beams[22]. So it was observed that peak and valley irradiated zones were indistinguishable in tumors within 24 h of MRT possibly because of a coordinated repair response[25].

Another radiobiological issue has to be addressed for MRT is radiation-induced bystander effects (RIBEs)[26], RIBEs have been broadly defined as the occurrence of biological effects in non-irradiated cells resulting from exposure of other cells to radiation. Bystander cells in exposed cell populations can be described as the non-irradiated cells that received signals from neighboring or distant irradiated cells. The molecular radiobiological mechanism still is under investigation. There were a few reports about the role of RIBEs in MRT, RIBEs (as DSB formation and micronuclei) in non-target normal cells like human fibroblasts could be observed after MRT[19], but it is still too early to conclude that RIBEs may be a source of additional stress for normal tissues in MRT modality. Since the impact of RIBEs is expected to diminish gradually as far as the distance from the targeted cells increases[27], it is not fully understood that RIBEs might be one of explanation for the necrosis and hypervascularity phenomena observed in the area (i.e. valley zone) close to tumor during MRT treatments[28].

It was observed that virtually identical absorbance patterns 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. It might be the first evidence for a mechanism by which MRT kills the whole tumor despite only a small percentage receiving peak irradiation[29]. In further 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. The findings demonstrated molecular differences in the tumor response to microbeam versus broad beam irradiation[30].

3.3.3 Application of MRT in the preclinical and clinical setting

Previous MRT experiments were essentially applied to the brain of adult rats, mice, duck embryos and piglets[31]. Although MRT resulted in improved therapeutic indices and efficient palliation, it often failed to eradicate those tumors completely. This led to the necessity of using MRT together 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 PVDR values in healthy tissue respect to the PVDR in the tumor and minimize of bone and brain valley doses[19,32-34]. MRT associated with a newly synthesized chemotherapeutic agent JAI-51 also increased the survival of 9LGS-bearing rats by inducing a cell cycle blockade in G2/M (p<0.01)[35]. Besides, MRT combined with a novel anti-angiogenic peptide, anginex increased the mouse mammary carcinomas (4T1) growth delay which was a moderately hypoxic and radioresistant tumor with propensity to metastasize[36].

Since the values of PVDR are higher than those predicted by previously published Monte Carlo simulation papers, PRESAGE dosimeters, using the fluorescence from a 638 nm laser on a confocal laser-scanning microscope that gives a much better spatial resolution than optical computed tomography[37], was used to quantitate the value of PVDR. Gamma-H2AX immunostaining, as a biodosimetric tool, was also used to evaluate in situ biological dose mapping within an irradiated tissue to trace microbeams and quantify DNA damage foci in valleys between beams following MRT treatment. This application of biological dose mapping approach can be to optimize MRT and estimate localized doses[38]. The pink beam (35-60 keV) produced by the ESRF was used to acquire *in vivo* imaging for the contour of the irradiated area developed for the radiosurgery of brain lesions in rats[39].

For forthcoming clinical trials, safe irradiation protocols in microbeam radiation therapy were defined by means of Monte Carlo simulations. Considering a unidirectional irradiation (field size of 2×2 cm^2) and a centrally located tumor, the largest peak and valley doses achievable in the tumor are 55 Gy and 2.6 Gy, respectively. The corresponding maximum valley doses received by the skin, bone and healthy brain are 4 Gy, 14 Gy and 7 Gy (doses in one fraction), respectively, i.e. those doses are within tolerances of the normal tissues (5% probability of complication within 5 years after treatment)[40].

Growing experimental evidence is showing that MRT can be a novel approach in the treatment of cancer. Submillimetric beams can be delivered following a stereotactic design bringing to the target doses in the range of hundreds of Gray without harm to the surrounding tissues, which means MRT may combine with SSRT. Microbeam arrays can be used to generate cortical transections or subcortical lesions, thus enabling the non-invasive modulation of brain networks. MRT is of great interest for the treatment of a variety of brain disorders, including functional diseases such as epilepsy and movement disorders[41].

4 Conclusion

The growth of new facilities of synchrotron radiation in the world is rapid. Synchrotron radiation has proved to have some unique advantages in terms of physical and biological aspects. It shows a great potential value to be applied in the treatment of cancer. Radioresistant cancer such as gliomas, inoperable brain tumor of children could be the targets of MRT, SSRT could be used for the treatment of tumors like lung cancer, hepatocellular carcinoma, etc. within short time since the tumor move frequently during fractionated irradiation due to respiration movement. With more knowledge of synchrotron radiation, it is playing an important role in clarifying therapy technology in the clinical application. Along with the SR-based radiotherapy clinical trials carried out across the world, synchrotron radiation will turn out as an excellent radiation source which can motivate the development of unique treatment modalities in the clinical settings of today.

Acknowledgements

The authors thank Prof. Zhao Zhentang and Prof. Xiao Tiqiao of the Shanghai Synchrotron Radiation Facility (SSRF).

References

1 Curtis H J. Radiat Res Suppl, 1967, **7:** 250−257.

2 Suortti P, Thomlinson W. Phys Med Biol, 2003, **48:** R1−35.

3 Robar J L, Riccio S A, Martin M A. Phys Med Biol, 2002, **47:** 2433−2449.

4 Corde S, Balosso J, Elleaume H. Cancer Res, 2003, **63:** 3221−3227.

5 Karnas S J , Yu E, McGarry R C. Phys Med Biol, 1999, **44:** 2537−2549.

6 Tange Y, Miyazaki M, Iwata J. Neurol Med Chir (Tokyo), 2009 , **49:** 572−579.

7 Gastaldo J, Bencokova Z, Massart C. J Synchrotron Radiat, 2011, **18:** 456−463.

8 Santos Mello R, Callisen H, Winter J. Med Phys, 1983, **10:** 75−78.

9 Rose J H, Norman A, Ingram M. Int J Radiat Oncol Biol Phys, 1999, **45:** 1127−1132.

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

11 Balcer-Kubiczek E K. Exp Oncol, 2012, **34:** 277−285.

12 Lee Y , Auh S L, Wang Y. Blood, 2009, **114:** 589−595.

13 Adam J F, Biston M C, Rousseau J. Phys Med, 2008, **24:** 92−97.

14 Edouard M, Broggio D, Prezado Y. Med Phys, 2010, **37:** 2445−2456.

15 Rousseau J, Boudou C, Barth R F. Clin Cancer Res, 2007, **13:** 5195−5201.

16 Yang W, Huo T, Barth R F. J Neurooncol, 2011, **101:** 379−390.

17 Renier M, Brochard T, Nemoz C. Eur J Radiol, 2008, **68:** S147−150.

18 Prezado Y, Fois G, Edouard M. Med Phys, 2009, **36:** 725−733.

19 Régnard P, Bräuer-Krisch E, Troprès I. Eur J Radiol, 2008, **68:** S151−155.

20 Siegbahn E A, Stepanek J, Bräuer-Krisch E. Med Phys, 2006, **33:** 3248−3259.

21 Crosbie J C, Svalbe I, Midgley S M. Phys Med Biol, 2008, **53:** 6861−6877.

22 Bräuer-Krisch E, Serduc R, Siegbahn E A. Mutat Res, 2010, **704:** 160−166.

23 Serduc R, Bräuer-Krisch E, Siegbahn E A. PLoS One, 2010, **5:** e9028.

24 Stone H B, Coleman C N, Anscher M S. Lancet Oncol, 2003, **4:** 529−536.

25 Crosbie J C, Anderson R L, Rothkamm K. Int J Radiat Oncol Biol Phys, 2010, **77:** 886−894.

26 Prise K M, O'Sullivan J M. Nat Rev Cancer, 2009, **9:** 351−360.

27 Hamada N, Matsumoto H, Hara T. J Radiat Res, 2007, **48:** 87−95.

28 Sprung C N, Cholewa M, Usami N. J Synchrotron Radiat, 2011, **18:** 630−636.

29 Sharma M, Crosbie J C, Puskar L. Int J Radiat Biol, Sep 10, 2012.

30 Sprung C N, Yang Y, Forrester H B. Radiat Res, 2012, **178:** 249−259.

31 Bencokova Z, Balosso J, Foray N. J Synchrotron Radiat, 2008, **15:** 74−85.

32 Prezado Y, Fois G, Le Duc G. Med Phys, 2009, **36:** 3568−3574.

33 Martínez-Rovira I, Prezadoa Y. Med Phys, 2011, **38:** 4430−4439.

34 Ghasemi M, Shamsaei M, Ghannadi M. Radiat Prot Dosimetry, 2009, **133:** 97−104.

35 Bouchet A, Boumendjel A, Khalil E. J Synchrotron Radiat, 2012, **19:** 478−482.

36 Griffin R J, Koonce N A, Dings R P. Radiat Res, 2012, **177:** 804−812.

37 Annabell N, Yagi N, Umetani K. J Synchrotron Radiat, 2012, **19:** 332−339.

38 Rothkamm K, Crosbie J C, Daley F. PLoS One, 2012, **7:** e29853.

39 Serduc R, Berruyer G, Brochard T. J Synchrotron Radiat, 2010, **17:** 325−331.

40 Martínez-Rovira I, Sempau J, Fernández-Varea J M. Phys Med Biol, 2010, **55:** 4375−4388.

41 Romanelli P, Bravin A. Neurol Res, 2011, **33:** 825−831.