Experimental verification of therapeutic doses for the superficially-placed tumor radiotherapy with heavy ions at HIRFL*

LIU Xin-Guo(刘新国)[1,2] LI Qiang(李强)[1;1)] WU Qing-Feng(吴庆丰)[1,2]
TAO Jia-Jun(陶家军)[1,2] JIN Xiao-Dong(金晓东)[1,2]

1 (Institute of Modern Physics, Chinese Academy of Sciences, Lanzhou 730000, China)
2 (Graduate University of Chinese Academy of Sciences, Beijing 100049, China)

Abstract Up to now, clinical trials of heavy-ion radiotherapy for superficially placed tumors have been carried out for six times and over 60 selected patients have been treated with 80—100 MeV/u carbon ions supplied by the Heavy Ion Research Facility in Lanzhou (HIRFL) at the Institute of Modern Physics, Chinese Academy of Sciences since November, 2006. A passive irradiation system and a dose optimization method for radiotherapy with carbon-ion beams have been developed. Experimental verification of longitudinally therapeutic dose distributions was conducted under the condition of simulating patient treatment in the therapy terminal at HIRFL. The measured depth-dose distributions basically coincide with the expected ones. These results indicate that the irradiation system and the dose optimization method are effective in the ongoing carbon-ion radiotherapy for shallow-seated tumors at HIRFL.

Key words heavy-ion radiotherapy, carbon ions, therapeutic dose verification, irradiation system, dose optimization

PACS 87.55.km, 87.56.-v, 87.55.D-

1 Introduction

The use of heavy ions (e.g. carbon ion) in radiotherapy is based on their two mainly favorable characteristics: physical and biological selectivities[1]. In the physical aspect, a heavy ion beam is characterized by an inverse depth-dose profile, i.e. a dose maximum (Bragg peak) presented at the end of the range. High doses, therefore, can be delivered to tumor targets while sparing surrounding healthy tissues so that unwanted and unnecessary side effects on tumor patients can be avoided as much as possible. On the other hand, a significantly enhanced Relative Biological Effectiveness (RBE), which is not shown in photon and even proton therapy, appears towards the Bragg peak region due to its high Linear Energy Transfer (LET) in the biological aspect. This makes heavy ion radiotherapy a promising modality for treating deeply-seated and radio-resistant tumors. Because of these superiorities of heavy-ion beams, many research groups joined in this field with their heavy ion accelerators (cyclotrons or synchrotrons) in America, Japan, Germany, China and other countries. Basic research on heavy-ion radiotherapy was started in 1995 at the Institute of Modern Physics (IMP), Chinese Academy of Sciences, and fruitful achievements have been obtained in terms of radiation physics, radiobiology and therapeutic technique[2]. A passive beam delivery system has been developed in the therapy terminal at HIRFL. At the same time, a dose optimization code for carbon ion therapy has been worked out. A first clinical trial of heavy-ion radiotherapy for superficially-placed tumors was carried out with 80.55 MeV/u carbon ions provided by the

Received 4 May 2008

* Supported by Century Program of Chinese Academy of Science (O506120BR0), and National High Technology Research and Development Program of China (863 Program, 2006AA02Z499)

1) E-mail: liqiang@impcas.ac.cn

Heavy Ion Research Facility in Lanzhou (HIRFL) in November 6th, 2006. Four patients were enrolled in the first clinical trial[3]. In the following clinical trials of five times (on Jan., Mar., Aug., Dec., 2007 and Mar., 2008) using 100 MeV/u carbon ions supplied by the HIRFL complex, about 60 patients with shallow-seated tumors have been treated in a manner of two-dimensional (2D) conformal irradiation in combination with layer stacking.

Apparently, delivering accurate doses to tumor targets is of extreme importance in radiation therapy. Therefore, it is absolutely necessary to confirm whether the doses delivered to a target satisfy the expected ones under the condition of simulating patient treatment, although some tests of the passive irradiation system and a three-dimensional (3D) conformal irradiation simulation with CR39 slices have been done in the therapy terminal at HIRFL[3, 4]. The implementation of our dose optimization method for carbon ion radiotherapy is briefly described and experimental verification of longitudinally therapeutic doses delivered by the irradiation system for patient plans generated with the dose optimization method is reported in this paper.

2 Materials and methods

The HIRFL complex, consisting of an ECR ion source, an injection cyclotron SFC (energy constant $K = 69$) and a main cyclotron SSC (energy constant $K = 450$), was built in the 1980s and now enables to accelerate ions from carbon to uranium with energy varying from a few MeV/u to 100 MeV/u[5]. A treatment room with a vertical beam port, two laser pointers in x and y directions for patient positioning and a treatment couch was constructed in 2005.

2.1 Irradiation system

Two kinds of beam delivery systems, i.e. active and passive beam shaping methods, are now available in the world. The HIRFL complex is a cyclotron supplying ions with constant energy. So a passive beam shaping method was adopted due to its simplicity. Our irradiation system consists of the passive beam delivery system and its relevant control system (see Fig. 1). As shown in Fig. 1, there are a series of typical devices in a passive system, including a ridge filter, a range shifter, a Multi-Leaf Collimator (MLC) and a compensator (not shown at the site of the No.2 big bold arrow) in the therapy terminal at HIRFL (see Ref. [5] for details).

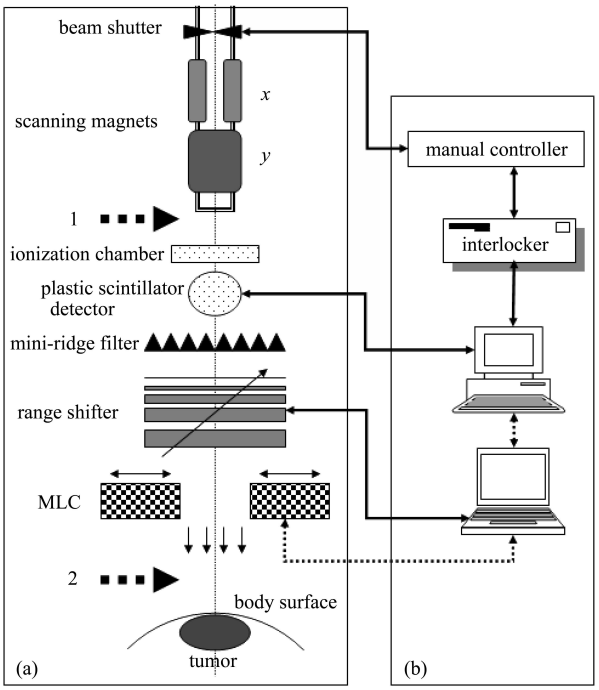

Fig. 1. A schematic diagram of the irradiation system installed in the shallow-seated tumor therapy terminal at HIRFL with a series of passive beam shaping devices in the treatment room (a) and an irradiation control system in the operating room (b). Dashed lines represent unachieved connections between devices. There are no a primary collimator and tumor specific compensators at the sites of No.1 and No.2 indicated by two big bold arrows.

In the period of therapy, x and y scanning magnets are supplied with 75 and 45 Hz zigzag periodic currents, respectively, to acquire a transversely uniform irradiation field. The homogeneity of the irradiation field is measured with a parallel plate avalanche counter[6] before treatment in the morning everyday. An ionization chamber and a plastic scintillator detector are utilized to monitor the beam intensity on-line, and signals from the plastic scintillator are converted to particle numbers. LabView programs[7], which were designed to show the beam intensity (particles per second) and to count the accumulated particles, trigger a feedback signal to the beam shutter to shut down the beam when the preset count is reached or an abnormal case happens.

At present no compensators are used in the treatment for superficially placed tumors at HIRFL, because there are usually no critical organs below these special tumors. Furthermore, a strategy of 2D conformal irradiation in conjunction with layer stacking is applied. A mini ridge filter (also called a ripple filter[8]), as shown in Fig. 1(a), is employed to extend a pristine sharp Bragg peak slightly so as to form a

Gaussian shaped mini Spread-Out Bragg Peak (mini-SOBP) like those used in the active scanning system at GSI[8] and the 3D layer-stacking conformal method at NIRS[9—11]. So the range shifter made of palymelhyl methacrylate shifts the mini-SOBP peak layer by layer to yield a desired dose distribution in depth together with controlling parameters coming from the dose optimization code. Laterally, the manual MLC is used to tailor the irradiation field according to the maximum contour of a target volume projected on a plane perpendicular to the beam direction. In this way, a variably uniform biological effective dose or a uniform physical dose can be delivered to the target volume using the present irradiation system.

2.2 Dose optimization method

The optimization of doses, especially biological effective doses, is very critical in radiotherapy with heavy-ion beams since their high biological efficiency. Relative Biological Effectiveness (RBE) defined as the dose ratio of the reference radiation to the heavy ions under consideration at the same effect level, has to be taken into account in the optimization of biological effective dose. Although the RBE value of a heavy-ion beam is related to many factors such as ion type, cell type, beam energy and so on, its LET (let) and the biological endpoint under consideration (usually cell survival level, sl) are the main determinants. Given a certain ion type (^{12}C ions) and cell type, RBE can be formulated by RBE(let, sl), and biological effective dose is defined as the product of RBE and physical absorbed dose as follows,

$$D_{\rm bio} = D_{\rm phy} \times {\rm RBE}(let, sl), \tag{1}$$

Whereas the RBE values measured by means of cell colony assays in which cells are irradiated with mono-energetic carbon-ion beam, cannot be used directly because a certain width of the SOBP region is irradiated with mixed LET carbon ions. The method of RBE calculation in a mixed LET ($let_{\rm mix}$) irradiation field which we are using was expatiated in Ref. [12]. Tabulated biological parameters, α and β coefficients in the linear-quadratic (LQ) model against LET obtained from colony assay of V79 cells irradiated with mono-energetic carbon-ion beam[13], are input to calculate the RBE value in a mixed LET carbon-ion irradiation field. Thus the biological effective dose is expressed as

$$D_{\rm bio} = {\rm RBE}(let_{\rm mix}, sl) \cdot \sum w_i d_i(let) \ , \tag{2}$$

where d_i and w_i are the i-th mono-energetic carbon-ion dose and its weight in the mixed field. Finally, the issue of the biological dose optimization is reduced to the problem of finding a solution to the following equation for w_i, where minimum value is reached for the equation:

$$\|\Delta\|^2 = \|D_{\rm bio}(x) - D_{\rm pre}(x)\|^2 = \sum_j \left\{ \left[{\rm RBE}(let_{\rm mix}(W), sl, x_j) \cdot \sum_i w_i d_i(x_j) \right] - D_{\rm pre}(x_j) \right\}^2, \tag{3}$$

where W denotes a solution set of w_i, x and x_j are the position of interest and check points in the SOBP region, respectively, and $D_{\rm pre}$ represents the prescribed dose given by a medical doctor. Therefore, mini-SOBP weights (i.e. solution sets of w_i), which are used to control the conformal irradiation to a target volume, are obtained. In addition, to obtain a uniform physical dose across a SOBP region, only physical doses are optimized regardless of the RBE variance (i.e. RBE is a constant value). The detailed optimization process and dose specification at IMP will be described elsewhere.

2.3 Dose verification

The verification of therapeutic doses using a carbon ion beam of 100 MeV/u was conducted in a way that absorbed doses in water, which is the main component of tissue, were measured under the condition of patient plans with a special configuration of water tank and ionization chamber. Due to the energy degradation of the vacuum window and air gap, the energy of the therapeutic beam was determined to be 95.1 MeV/u at the iso-center according to the location of the Bragg peak in water (23.2 mm). In the patient plans, the expected SOBP widths and layer thickness were defined to be 1 cm and 2 mm, respectively. So six mini-SOBP peaks would be needed to sweep the expected SOBP region. The weights of the 6 mini-SOBP peaks and their physical doses at the peak positions derived from the dose optimization method above are given in Table 1 for two kinds of dose distributions, i.e. the uniform physical absorbed dose 1 Gy and the uniform biological effective dose 2.8 GyE in the SOBP region.

Before determining how many particles should be delivered for each mini-SOBP peak, a pre-experiment performed in the morning of the therapy day was done to determine the dose calibration factor (8.61×10^7 ions/Gy for this verification experiment) for the beam monitors in the irradiation system. Thus the particle preset number for every mini-SOBP peak is determined by the product of the dose calibration factor and its corresponding physical dose (see Table 1).

Table 1. The weights and physical doses of the mini-SOBP peaks to form uniform physical (1 Gy) and biological effective (2.8 GyE) dose distributions for a 1 cm width SOBP.

No. of	$D_{\rm phy}$		$D_{\rm bio}$	
mini-peaks	weight	dose	weight	dose
1	1	0.983397	1	0.5503
2	0.371734	0.365562	0.609868	0.335611
3	0.264176	0.25979	0.525661	0.289271
4	0.215352	0.211776	0.482242	0.265378
5	0.184788	0.18172	0.450003	0.247637
6	0.163806	0.161086	0.430256	0.23677

Note: The data in the $D_{\rm phy}$ column were used for the uniform physical dose distribution and $D_{\rm bio}$ column for the uniform biological effective dose distribution in the 1 cm width SOBP.

A commercial standard ionization chamber (PTW/Markus-23343, sensitive volume 0.055 cm^3, Germany) driven by a stepping motor in a water tank and a dosimeter (PTW/UNIDOS, Germany) were used to measure the absorbed doses in water at different depths. For each depth, the complete layer-stacking irradiation process was carried out once.

3 Results and discussion

Figure 2(a) shows the measured and calculated depth-dose distributions for the patient plan of 1 Gy uniform physical absorbed doses across the 1 cm SOBP. The calculated depth-dose distributions (curve and cross points that are shown in Fig. 2(a)) were derived from the dose optimization method, where two different datasets were used. One was the calculated data of the deepest mini-SOBP in which the depth-dose distribution of the 95.1 MeV/u carbon-ion beam computed by the HIBRAC code[14] was modified by the parameters of the mini ridge filter. The other one was the measured data of the deepest mini-SOBP at the HIRFL therapy terminal. In the calculations, the two deepest min-SOBP datasets were respectively shifted forwards layer by layer according to the corresponding weights (see the $D_{\rm phy}$ column in Table 1) to form the 1 cm SOBP. The fact that many dose points calculated by the latter dataset fell on the curve derived from the former dataset, as shown in Fig. 2(a), indicates that the two input datasets were matched well and shows indirectly that the mini ridge filter produces a Gaussian shaped mini-SOBP. It is clear that the measured dose points (open circle shown in Fig. 2(a)) basically coincided with the two calculated results, although some divergences occurred in the SOBP region. Note that the measured data are all less than 1 Gy across the SOBP. Partially the reason is that we missed the depths in which the component mini-SOBP peaks were during the measurement. On the other hand, the mini-SOBP peak slightly extended from the pristine Bragg peak of the 95.1 MeV/u carbon-ion beam is narrow; thereby extremely dose fluctuations are presented in the optimization result with the layer spacing of 2 mm. In addition, we expected the doses only at the mini-SOBP peaks equal to 1 Gy, thus the doses at most depths would be less than 1 Gy. If we define the divergence as follows,

$$\delta = \left|1 - \frac{D_{\rm measured}}{D_{\rm calculated}}\right| \times 100\% \ , \qquad (4)$$

then the average deviation of the measured data (not included the last measured dose point) from the calculated curve is 4.1%. We think that this is sufficient for the current radiotherapy of superficially placed tumors.

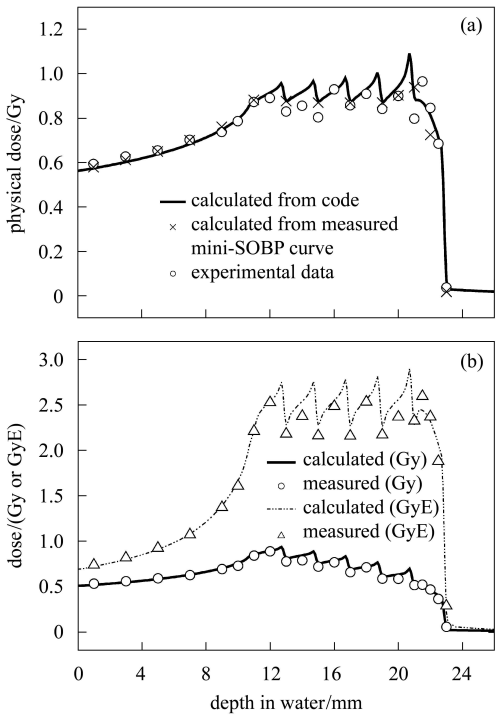

Fig. 2. The measured and calculated depth dose distributions in the two cases of uniform physical dose 1 Gy (a) and uniform biological effective dose 2.8 GyE (b) expected in a SOBP region of 1 cm width.

For the patient plan of uniform biological effective dose 2.8 GyE across the 1 cm SOBP, α and β parameters in the LQ model for V79 cells irradiated with X-rays and carbon ions[13] as biological data were input to the optimization process and the expected biological effective dose value in the SOBP region. Then the physical absorbed dose, biological effective dose, cell

survival levels, dose averaged LET and RBE distributions in depth were obtained. Shown in Fig. 2(b) are the calculated and measured physical and biological effective dose distributions in depth. It should be pointed out that the measured biological effective doses were derived from the product of the measured physical doses and the calculated RBE values. The average divergences of the measured physical doses and biological effective doses (not included the last measured dose point) compared to the respective expected results are the same, namely 3.5%. This is so because the same RBE dataset was used in the determination of the measured and calculated biological effective doses. Owing to larger RBE at lower doses, the actual biological effective doses in the SOBP region are estimated to approach to the desired ones with a deviation of less than 3.5%. However, this point remains to be evaluated in the future cell radiobiological experiment aiming at the verification of biological effective doses. In fact, the only verification approach is the use of cell colony assays in which cell survival levels are measured under certain treatment configurations[12, 15—17].

As shown in Fig. 2, the measured data at the plateau region were in good agreement with the calculated ones. However, in the SOBP region most of the measured doses were slightly less than the calculated ones for both the patient plans. This would be caused by the multiple scattering effects in the thicker range shifter when the depth increased. So the multiple scattering effects should be included in our future dose optimization method.

In any event, good agreement between the measured and planned therapeutic doses was obtained in the verification experiment. Nevertheless, some improvements to the irradiation system and the dose optimization method should be made in the near future. There should be a primary collimator set in the upstream of the beam delivery system (indicated by the No.1 big bold arrow in Fig. 1(a)) in order to get a more uniform irradiation field. To reduce the dose fluctuation across a SOBP, more mini-SOBP peaks should be used to form the desired SOBP. This means that more treatment time and a more precise irradiation control system are needed. Obviously, a better compromise strategy should be considered. In addition, as shown in Fig. 2 the width of the high dose region (i.e. the desired SOBP) is slightly larger than 1 cm, although the distance between the first and last mini-SOBP peaks which are needed to form the desired SOBP is equal to 1 cm. Therefore, a reasonable definition of SOBP width also should be put forward so that the number of layers is determined definitely for the treatment of superficially placed tumors.

4 Conclusion

Depth dose distributions of patient plans were measured under the condition of simulating patient treatment using a therapeutic carbon-ion beam in the shallow-seated tumor therapy terminal at HIRFL. The measured data basically coincided with the expected dose distributions derived from the dose optimization method, which now we are using for patient treatment. This experimental verification indicates that both the irradiation system and the dose optimization method are valid for the ongoing treatment of superficially-placed tumors with carbon ions at HIRFL though some improvements should be made.

References

1 Kraft G. Prog. Part. Nucl. Phys., 2000, **45**: S473
2 LI Q. Adv. Space Res., 2007, **40**: 455
3 ZHANG H, LI S, LI Q et al. First Clinical Trial of Cancer Therapy with Heavy Ions at IMP. IMP & HIRFL Annual Report, Beijing: Atomic Energy Press, 2006. 83
4 DAI Z Y, LI Q, YAN Z et al. HEP & NP, 2006, **30**(9): 920 (in Chinese)
5 DAI Z Y, LI Q, XIAO G Q et al. HEP & NP, 2007, **31**(7): 655 (in Chinese)
6 LI Q, DAI Z Y, YAN Z et al. Med. Bio. Eng. Comput., 2007, **45**(11): 1037
7 TANG B et al. Nuclear Electronics & Detection Technology, 2008,**28**(4): 699 (in Chinese)
8 MAO R S et al. High Power Laser and Particle Beams, 2008, **20**(9): 1537 (in Chinese)
9 Weber U, Kraft G. Phys. Med. Biol., 1999, **44**: 2765
10 Futami Y, Kanai T, Fujita M. Nucl. Instrum. Methods Phys. Res. A, 1999, **430**: 143
11 Schaffner B, Kanai T, Futami Y. Med. Phys., 2000, **27**(4): 716
12 Kanematsu N, Endo M, Futami Y. Med. Phys., 2002, **29**(12): 2823
13 Kanai T, Furusawa Y, Fukutsu K. et al. Radiat. Res., 1997, **147**: 78
14 Furusawa Y, Fukutsu K, Aoki M. et al. Radiat. Res., 2000, **154**: 485
15 Sihver L, Schardt D, Kanai T. Jpn. J. Med. Phys., 1998, **18**(1): 1
16 Mitaroff A, Kraft-Weyrather W, GeiB O. et al. Radiat. Environ. Biophys., 1998, **37**: 47
17 Kramer M, WANG J F, Weyrather W. Phys. Med. Biol., 2003, **48**: 2063
18 Kanai T, Endo M, Minohara S et al. Int. J. Radiat. Oncol. Biol. Phys., 1999, **44**(1): 201