J. Radiat. Res., 48: Suppl., A97-A102 (2007)

Comparison of the Methods of Specifying Carbon Ion Doses at NIRS and GSI

John GUEULETTE* and André WAMBERSIE

Carbon ions/Carbon-therapy/Biological treatment plan/RBE.

Due to the RBE variations, the carbon-ion doses (in Gy) are no longer sufficient to monitor adequately the biological effect of these radiations. Therefore, "RBE dose weighting factors" - W_{RBE} - allowing for the RBE variations with energy, dose and biological system have to be introduced in the treatment plans in order to provide the physician with interpretable information. This paper compares the methods employed for this purpose at NIRS and GSI, which are specific of the beam delivery system of these institutions. NIRS has a "passive" beam delivery system where the dose distribution in the SOBP is determined by a Ridge filter. The dose distribution - and thus, the shaping of the filter - is chosen according to the clinical situation and determined with respect to W_{RBE} factors in order to yield a biologically iso-effective SOBP. W_{RBE} factors in the SOBP are at first derived from a RBE/LET function for HSG cells, then normalized to 3 at a LET of 80 keV/μm. The latter value of 3 corresponds to the clinical RBE of NIRS-neutrons, which were found to exhibit the same radiobiological properties as 80 keV/μm carbon-ions. GSI has a "dynamic" beam delivery system ("spot" or "voxel" scanning) making it possible to irradiate irregular volumes and to modulate the radiation intensity according to the radiosensitivity of different tissues and/or different sub-volumes. Due to the "power" and the resulting complexity of the system, W_{RBE} factors are determined through an integrated calculation code allowing iterative interaction of both physical and radiobiological parameters. The "Local Effect Model" (LEM) was developed in this view with the aim of deriving carbon-ion W_{RBE} factors from the parameters determining the response to photons. Advantages and weaknesses of the respective methods will be discussed.

INTRODUCTION

Clinical application of hadron beams has raised several new problems related to treatment planning systems. First, the RBE of hadrons (especially for light ions) is substantially higher than that of photons : the radiation oncologist is thus confronted with substantially smaller therapeutic doses (in Gy) than those he is used to apply with photons. Second, the radiosensitivity differences between tissues and/or irradiation conditions might be modified in comparison with photons : the radiation oncologist has to "rebuilt" his radiobiological/clinical experience. Third, RBE varies with energy and/or depth (especially for light ions and in a lesser extent for protons) : iso-doses (in Gy) in a given tissue do no necessarily correspond to biologically iso-effective doses.

As a result, the classical treatment plans based on physical iso-doses can no longer be used and have to be reconsidered in order to provide the radiation oncologist with interpretable information. The manner of allowing for the above problems depends essentially on the method of beam delivery. This paper will compare the methods used at the National Institute for Radiological Sciences (NIRS) in Chiba (Japan) using a "passive" beam delivery system and at the Gesellschaft für Schwerionenforschung mbH (GSI) in Darmstadt (Germany) using a "dynamic" system.

*Corresponding author: Phone: +32-2-764-54-80,
Fax: +32-2-764-94-25,
E-mail: john.gueulette@imre.ucl.ac.be
Université catholique de Louvain, Laboratoire d'Imagerie Médicale et de Radiothérapie Expérimentale (IMRE-5469), 54 Avenue Hippocrate, 1200 Brussels, Belgium.

PASSIVE BEAM DELIVERY SYSTEM AT NIRS

Background

The term "passive" refers to the fact that - due to the particular design of the beam delivery system (Fig. 1) - the physical characteristics of the beam (*e.g.* energy, intensity, depth/dose profile) cannot be changed and have to be maintained during an entire irradiation session. Offering no flexibility (especially in the depth/dose profiles), these beams have thus to be shaped "in advance" in order : 1) to have a penetration (*i.e.* initial energy) in accordance with the depth of the tumor, and 2) to yield a biologically iso-effective dose over the desired distance (width of the SOBP).

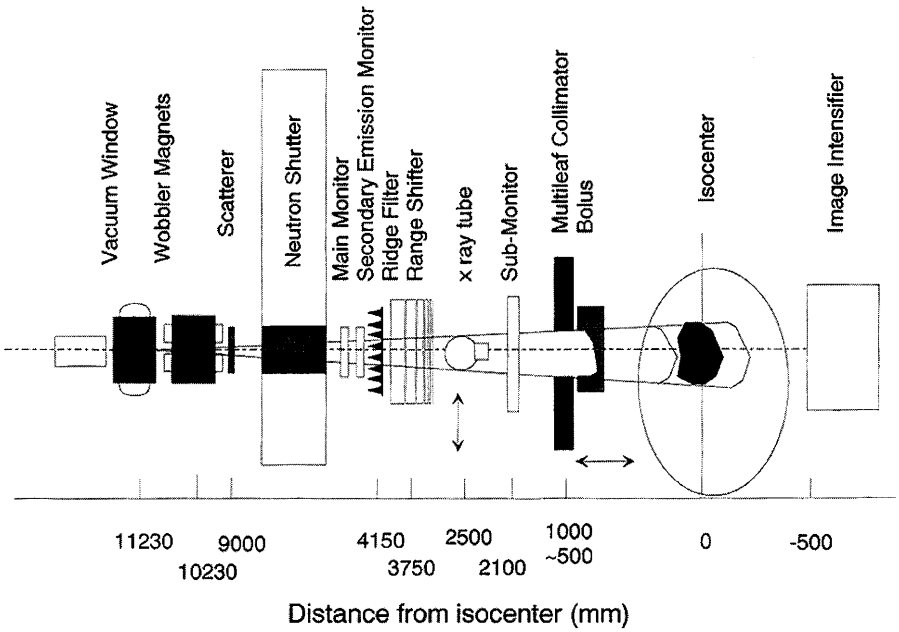

Fig. 1. Irradiation system at the HIMAC facility. From Kanai *et al.*.[1)]

The first requirement (penetration) is allowed for relatively easily as it only implies a physical action consisting in interposing in the beam the appropriate range filter. Such is not the case for the second requirement (biologically iso-effective SOBP) which necessitates the use of a Ridge filter featuring characteristics whose determination resort to both physics and radiobiological considerations. The next section will describe how RBE data are taken into account and introduced in the calculations determining the Ridge filter design. Note that the term "Clinical RBE" employed in this section will be meant as the ratio of the dose that would have been given with photons and the dose actually given with carbon, for the same clinical situation. On the other hand, the photon-equivalent doses will be expressed in "GyE" in order to comply with common practice and avoid any ambiguity.

From physical dose (in Gy) to photon equivalent dose (in GyE)

Let us start from a concrete example and summarize how and under which hypothesis the physical dose distribution (in Gy) presented in Fig. 2 was determined in order to (biologically) flatten the SOBP and yield at this level a 2.7 GyE photon-equivalent clinical dose. Consider first the RBE/dose averaged LET variation (Fig. 3) and notice that the RBE of HSG and HeLa cells for carbon coincides with the NIRS neutron RBE (for the same cells) around a LET value of 80 keVμm (RBE = 2). It is then assumed that NIRS neutrons are equivalent to NIRS carbon at a LET 80 keV/μm, which value is reached in the present carbon beam (290 MeV/u) 8 mm upstream the distal edge of the 6-cm SOBP (see in Fig. 2). Applying that RBE value (RBE = 2) to that position and correcting the doses for the other positions according to the RBE/LET variation of Fig. 3, a (first) virtual 1.8 GyE photon-equivalent biologically iso-effective region is obtained in the SOBP.[2)] A second assumption has now to be made for converting the former "*in vitro*" photon equivalent doses into "clinical" photon equivalent doses. This assumption is based on that NIRS neutrons were safely applied using a clinical RBE of 3, which value was then retained for carbon at the reference LET of 80 keV/μm. So, the ratio between the clinical RBE of the NIRS neutrons and the RBE of HSG/HeLa cells for 80 keV/μm (*i.e.* 3 / 2 = 1.5) was used, which allowed to pass from the (virtual) *in vitro* photon-equivalent dose of 1.8 GyE to the *clinical* photon equivalent dose of 2.7 GyE (*i.e.* 1.8 GyE × 1.5 = 2.7 GyE).

Actually, the process is made in the reverse order : the GyE clinical dose is determined at first by the physician, what - applying the neutron clinical RBE of 3 - determines the physical dose (in Gy) in the SOBP at the reference position (8 mm upstream the distal edge). The doses at the other positions (*i.e.* the design of the Ridge filter) are then determined using the RBE/dose averaged LET variation of Fig. 3. Important to note that the "clinical RBE" at the *center of the SOBP* (point of dose specification) is smaller than 3 (clinical RBE = 2.4) as the physical dose at this point was increased to allow for the HSG/HeLa cells RBE variations. In addition, as the LET at the center of the SOBP increases when the width of the SOBP decreases (and gives rise to higher RBEs), specific clinical RBEs have to be defined for the various sizes of SOBPs (values ranging from 2.1 to 2.8 are used for SOBP widths ranging from 120 mm to 30 mm). Finally, let us draw the attention towards the fact that the

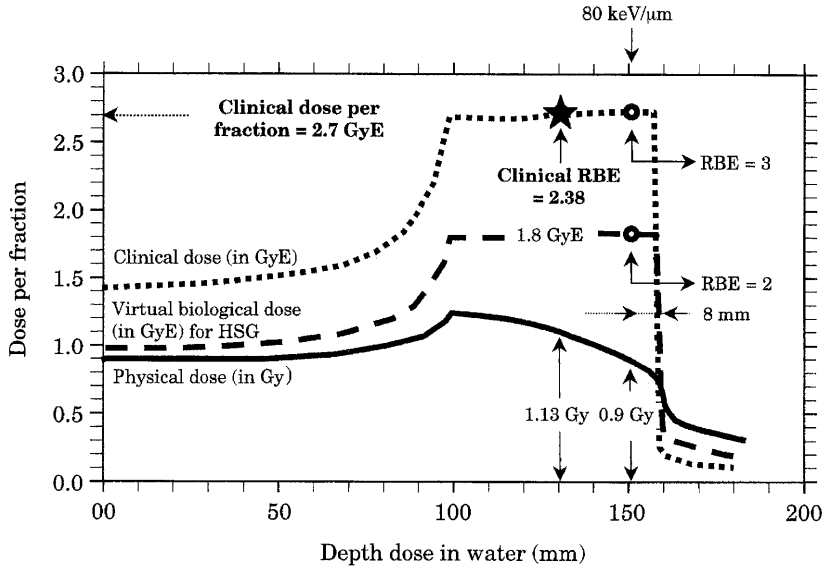

Fig. 2. Physical and photon-equivalent depth-dose distributions in a 290 MeV/u carbon beam (6-cm SOBP). See text. Redrawn from Kanai *et al.*.[1)]

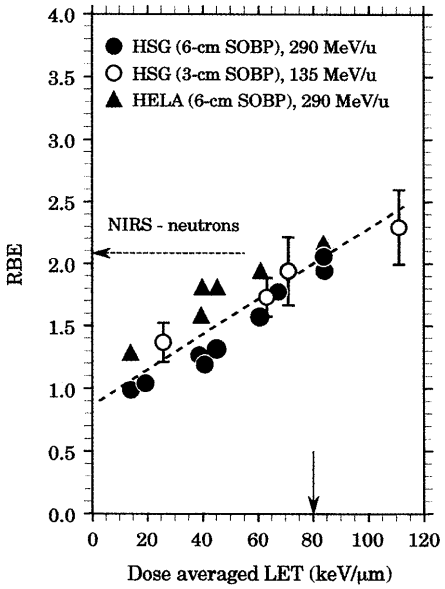

Fig. 3. RBE / LET variation for colony formation of Human Salivary Gland (HSG) and HeLA cells at a 10% survival level in carbon beams of different energies and different SOBPs. Redrawn from Kanai *et al.*.[1)]

clinical RBE of the NIRS carbon beam is substantially different than 3 (NIRS neutron RBE), which value is however understood by unfamiliar radiation oncologists as being the clinical RBE at the point of dose specification, regardless of the shaping of the beam.

ACTIVE BEAM DELIVERY SYSTEM AT GSI

Background

The term "active" (or "dynamic") refers to the fact that these systems are constructed in such a way (Fig. 4) that the beam can be shaped "on line". In contrast with passive beam delivery systems, active systems (*e.g.* spot- or voxel-scanning) make it possible to irradiate irregular volumes and to modulate the radiation intensity in order to allow for the radiosensitivity differences (RBE differences) between tissues and/or subvolumes. Due to the "power" of the system and its resulting complexity, the problem of introducing radiobiological data into the dose determinations cannot be

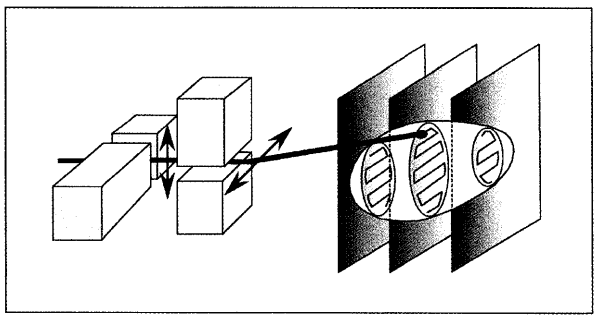

Fig. 4. "Principle of the active raster scan system used at GSI for carbon ions. A small pencil beam is scanned in vertical and horizontal direction by using 2 pairs of scanner magnets. By switching the energy of the synchrotron, the position of the Bragg peak can be chosen so that each scanned area is adapted to the extent of the target in depth". Redrawn, and legend from Schulz-Ertner *et al.*.[3)]

restricted to the input of "simple" RBE values (*i.e.* for a reference tissue and reference conditions) nor on the consideration of "simple" dose or LET distributions as those that could be predicted from *e.g.* initial energy and characteristics of the Ridge filter. Therefore, an integrated calculation code allowing iterative interaction of both physical and radiobiological data was developed. The model used for determining the radiobilogical parameters will be described in the next section.

The Local Effect Model (LEM)

This model (Scholz and Kraft, 1994[4]) aims at deriving the parameters determining the biological response to carbon ions (or to any charged particle) from those determining the response to photons. There are two fundamental hypothesis : 1) the critical radiosensitive structures whose damage leads to cell inactivation are solely contained in the cell nucleus , and 2) the probability of damaging these structures depends solely on the energy deposition in that structures and is independent on the particular radiation type leading to that energy deposition. Consequently : 1) the difference between carbon and photons should be attributed to the difference in spatial energy deposition patterns, and 2) the biological response to carbon should be derivable from that of photons. Therefore 3 pieces of information are needed : 1) photon dose-response curves (for determining the probability of the occurrence of a damage), 2) physical data describing the track structures (for determining the corresponding "local

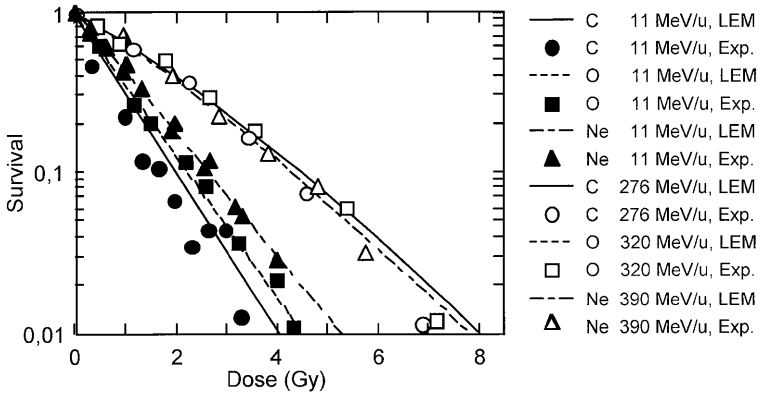

Fig. 5. Comparison of experimental data and prediction of LEM for different charged particles and different energies. From Krämer *et al.*.[5] Published with permission from : The increased biological effectiveness of heavy charged particles; from radiobiology to treatment planning. Technology in cancer research & treatment 2 (5): 432 (2003). http://www.tcrt.org

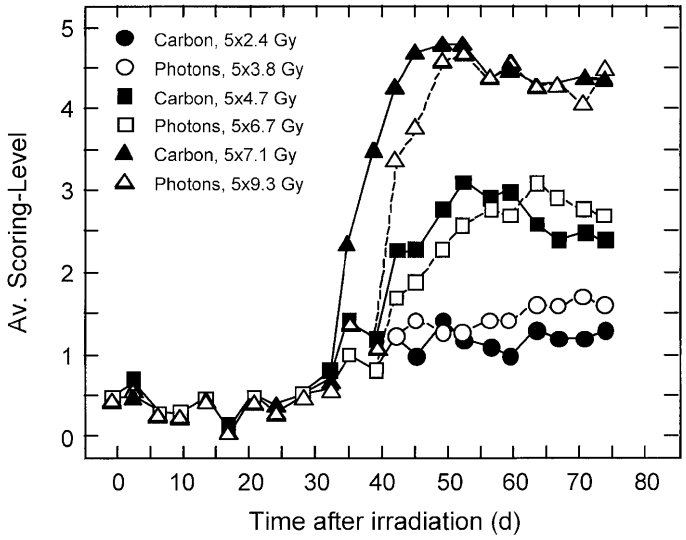

Fig. 6. Skin reactions on pigs after photon (dotted lines, open symbols) and carbon ions (plain line, closed symbols). From Krämer *et al.*.[5] Published with permission from : The increased biological effectiveness of heavy charged particles; from radiobiology to treatment planning. Technology in cancer research & treatment 2 (5): 433 (2003). http://www.tcrt.org

dose depositions") and 3) experimental measures of the cell nucleus (for determining the size of the area for possible damages).

In a first step, these information are provided by photon cell survival curves *in vitro*, which can be determined relatively easily for a wide range of cell types. The model was found to work well and, as shown on Fig. 5, is able to predict the *in vitro* response to different ion beams for a wide energy range.

The second step deals with the choice of the parameters of cell inactivation accounting for the *clinical* response (*i.e.* for tissues or organ). This choice is based on the assumption that biological end-points exhibiting the same α/β ratio for photons should exhibit the same RBE for a given type of radiation. The cell inactivation parameters accounting for the clinical response are thus chosen as being those of the photon cell survival curves in-vitro exhibiting the same α/β ratio as the tissues under consideration. The latter tissue ratios for photons are determined from clinical studies for the considered endpoints, or, when not available, from *in vivo* studies. The procedure above was found secure and to exhibit a precision compatible with that required for clinical applications (Fig. 6). It is an ingral part of the treatment planning system currently used at GSI.

DISCUSSION

Concerning NIRS

If the possibilities of improving the dose distributions and optimizing the treatments are relatively limited with passive beam delivery systems, their "rigidity" may be seen as an advantage for prescribing and reporting the treatment. Indeed, concerning the dose prescription, the use of a single clinical RBE value (for a given clinical situation) enables the radiation oncologist to catch on - easily and consistently - his judgment to his experience with photons (a minimum "radiobiological culture" is however required, especially to allow for the RBE differences between tissues or subvolumes). These advantages have repercussions in the treatment report, where a limited information should thus permit to describe the treatment procedure adequately. The minimum information are :

- initial energy of the carbon beam and characteristics of the range filter,
- physical dose distribution (in Gy),
- clinical RBE at the point of dose specification,
- prescribed dose (both physical (in Gy) and photon-equivalent doses (in GyE)) and its point of specification,
- some physical parameters (*e.g.* LET) describing the radiation quality at critical points of the depth-dose profile (*e.g.* initial plateau, beginning middle and end of the SOBP).

On the other hand, the manner of accounting for RBE might raise several questions. For example, what is the strategy when reference to the clinical RBE of neutrons (RBE = 3) is obviously inadequate for the actual clinical situation, and what are the repercussions of the change of clinical RBE on the flattening of the SOBP ? Concerning SOBP flattening, are there clinically relevant data validating that the biologically iso-effective SOBP obtained with HSG cells in culture reflects in a biologically iso-effective SOBP for the tumors in clinical situation (fractionation and small doses per fraction) ? Other questions may be raised, for example : how to deal with the necessary change of dose resulting from an unexpected change in the overall treatment time or in the number of fractions ; or, what are the possibilities of using different beam ports in the course of a single irradiation session ? The response to these questions will certainly give raise to valuable comments and be the source of constructive ideas.

Concerning GSI

The manner of accounting for RBE and its variations is essentially governed by the characteristics of the beam delivery system where "*several thousands of narrow ion pencil beams with individual lateral positions, ion energies and particle fluences are combined to form an intensity-modulated field of high granularity*" (Krämer, 2001[6]). In this view, it is difficult to imagine how another type of model than the LEM could offer the possibility of exploiting the potential "biological" advantages of the spot-scanning system. As a matter of fact, allowance can be made for RBE variations resulting from either physics related factors (*e.g.* variation of radiation quality in depth) or from biological related factors (*e.g.* intrinsic radiosensitivity, dose level, etc.), which would, in principle, permit to make the treatment "tumor or patient specific". The price to pay is a certain degree of "opacity" and the necessity for the radiation oncologist to trust the treatment plans without any easy possibility of making his mind about the biological options and underlying hypothesis. In turn, as listing all the parameters and sinking in the intricate pattern of the treatment planning code is unfeasible for practical reasons, the method for reporting the treatment is not straightforward. In this regard, dealing with some biological parameters (*e.g.* α/β ratios) and some physical information (*e.g.* absorbed dose distribution) might be relatively easy. But, for example, how to sum up the variation of the radiation quality (which information is however indispensable for interpreting the value of the biological parameters) ?

The concerns about LEM are generally not the bases of the model, but the way and the hypothesis made for handling these bases. Such is the case for *e.g.* the determination of the local dose distribution (*e.g.* parameter r_{min}), the fit of experimental photon data (parameter d_t), cross sectional area of the nucleus nucleus, etc. These have been discussed extensively by the authors[7] who clarified the misunderstandings while recognizing the possibility of optimizing some param-

eters or refining some aspects of the method. They also gave different illustrative examples justifying the use of the present model for clinical application.

Biological treatment plan philosophy

Determinations of radiation quality and absorbed dose distributions are pure physics problems resorting to experimentation, codes and calculations. They won't be considered here, nor the delineation of target volumes, sub-volumes, margins, etc., which are pure medical problems resorting to imaging techniques and medical appreciation. Combined with biological evidences provided by specific imaging methods (*e.g.* detection of oxygenation) the whole of these information constitute the "input data" which are specific of the type of beam and the clinical situation.

In principle, the physical dose D (in Gy) at each point of the irradiated volume has to be weighted by a "RBE weighting factor", W_{RBE},[8] allowing for :

- the RBE variation with radiation quality,
- the RBE variation with dose,
- the RBE variation with biological system (type of tissue and physiological status).

The product of the absorbed dose by the RBE weighting factor (*i.e.* $D \times W_{RBE}$) yields the so called "photon equivalent dose" (usually expressed in GyE) whose distribution over the irradiated volume constitutes the "biological treatment plan" that reflects the photon-equivalent therapeutical strategy of the physician. (Easy change of input data (*e.g.* degree and limit of an hypoxic area) and quick computation of the corresponding plans appear mandatory as they would enable the physician to test different options and optimize his strategy).

W_{RBE} factors would be derived from different RBE/LET and RBE/dose functions for different well-selected biological systems and irradiation conditions. They could be determined through a code (like in the LEM model) or using databases and lists from literature. From a pragmatic point of view, the W_{RBE} values at the point of dose specification (*e.g.* the center of the SOBP) would correspond to the "clinical RBE", *i.e.* the parameter that the physicians are used to consider to figure out the response to a new type of radiation. Similar clinical RBEs could be defined for other volumes or sub-volumes, notably for the tissues at risk. In this regard, note that there are no "true" RBE values and thus no true W_{RBE} factors since their determination could be based on different equally relevant hypothesis. Their choice depends - and has to depend - on the judgment of the clinicians who should thus be clearly informed. Therefore it would be advisable to mention on the treatment plan the clinical RBEs (in the above sense) for each tissue or sub-volume considered, which would also constitute a quick quality assurance check.

Whatever the strategy, the above RBE/LET and RBE/dose functions should be validated through specific carbon experiments for a number of selected cell lines and selected *in vivo* models accounting for the late and/or early tolerance of normal tissues. In addition, each individual carbon beam should be radiobiologically calibrated for a reference biological system and reference conditions, which is necessary to allow for the "machine specific" RBE variations and to compare the biological plans from different institutions.

REFERENCES

1. Kanai, T., Endo, M., Minohara, S., Miyahara, N., Koyama-ito, H., Tomura, H., Matsufuji, N., Futami, Y., Fukumura, A., Hiraoka, T., Furusawa, Y., Ando, K., Suzuki, M., Soga, F. and Kawachi, K. (1999) Biophysical characteristics of HIMAC clinical irradiation system for heavy-ion radiation therapy. Int. J. Radiation Oncology Biol. Phys. **44** (1): 201–210.
2. Furusawa, Y., Fukutsu, K., Aoki, M., Itsukaichi, H., Eguchi-Kasai, K., Ohara, H., Yatagai, F., Kanai, T. and Ando, K. (2000) Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated (3)He-, (12)C- and (20)Ne-ion beams. Radiat Res. **154** (5): 485–496.
3. Schulz-Ertner, D., Jäkel, O. and Schlegel, W. (2006) Radiation therapy with charged particles. Seminars in Radiation Onclogy **16** (4): 249–259.
4. Scholz, M. and Kraft, G. (1994) Calculation of heavy ion inactivation probabilities based on track structure, X-ray Sensitivity ant target size. Radiat. Prot. Dosim. **52**: 29–33.
5. Krämer, M., Weyrather, W. K. and Scholz M. (2003) The increased biological effectiveness of heavy charged particles; from radiobiology to treatment planning. Technology in cancer research & treatment **2** (5): 427–436.
6. Krämer, M. (2001) Treatment planning for heavy-ion radiotherapy: biological optimization of multiple beam ports. J. Radiat. Res. **42**: 39–46.
7. Scholz, M. and Kraft, G. (2004) The physical and radiobiological basis of the local effect model: a response to the commentary by R. Katz. Radiat Res. **161** (5): 612–620.
8. Wambersie, A., Gahbauer, A. R. and Menzel, G. H. (2004) RBE and weighting of absorbed dose in ion-beam therapy. Radiother Oncol. **73** Suppl 2: S176–S182.

Received on February 1, 2007
Revision received on February 26, 2007
Accepted on March 9, 2007