EDITORIAL

Radiotherapy for brain tumors –
New techniques and treatment strategies

Anca-Ligia Grosu, Franziska Fels

Department of Radiation Oncology, University Hospital Freiburg, Germany

Correspondence: Anca-Ligia Grosu. Address: Department of Radiation Oncology, University Hospital Freiburg, Germany. Email: anca.grosu@uniklinik-freiburg.de

Received: November 14, 2011 **Accepted:** December 24, 2011 **Published:** February 1, 2012
DOI:10.5430/jst.v2n1p1 **URL:** http://dx.doi.org/10.5430/jst.v2n1p1

Radiotherapy is generally a local treatment. The radiation oncologist marks image-based the area to be irradiated (target volume) as well as areas which should be spared (organs at risk). Three important volumes differ in marking of the target volume: gross tumor volume, clinical target volume and planning target volume. Gross tumor volume (GTV) means the volume where tumor is traceable in CT, MRI, ultrasonic sound, PET or clinical inspection and palpation. Clinical target volume (CTV) involves the GTV and the microscopic tumor expansion: peritumoral regions, lymph nodes, perineural or perivascular tumor infiltration, etc. The Planning Target Volume includes the CTV as well as the possible mobility of the tumor and the imprecision in positioning of patients at the linear accelerator. With an exact positioning of the patient at the irradiation device, PTV margin can be considerably reduced. That leads to a reduction of exposure in the healthy tissue and to a dose weighting in the tumor area.

Technological development of the last few years is characterized by three intentions:

1. -Better illustration of the tumor and the organs of risk with imaging
2. -Preciser gathering of the target volume with new treatment planning systems
3. -Exacter positioning of the patient at the irradiation device

Biological imaging for target volume definition

The traditional target volume definition for treatment planning results from CT and MRI. These examinations present the anatomy of the tumor and the normal tissue with a high resolution and admit a three-dimensional, conformal treatment planning. Disadvantage of these methods is that they show, in few patients, tumor and healthy tissue in the same density/intensity, that they can usually not distinguish post therapeutic changes of the tumor tissue and give no information about the biological nature of the tumors.

For example, after a primary resection of a high-grade glioma in sano, blood brain barrier impairment is observed, which is caused by the operation per se and can present itself in CT- or MRI-imaging like a residual or relapse of the tumor. In this situation, the demarcation of the macroscopic tumor (GTV) for treatment planning is often difficult. Another example are the gliomas after radio-chemo-therapy: In some patients, an increase of contrast uptake during adjuvant chemotherapy with Temozolomid is observed, which is regredient in the course of time and can be misinterpreted as tumor progression. This phenomenon was characterized as pseudoprogression [1]. In contrary, after treatment with Avastin/Bevacizumab, a remission of the barrier impairment and the oedema can be seen, which suggests a tumor remission in MRI or CT even though the tumor is still growing. This phenomenon is called pseudoremission [2]. The impreciseness in the description of

the GTV hinders the radiation oncologist in a precise definition of the target volume for treatment planning and leads to the fact that new image-guided methods have to be found, which make the differentiation between tumor tissue and healthy tissue with higher sensitivity and specificity.

MET- and FET-PET have a higher exactness in the differentiation of tumor tissue

An examination to differentiate malign and benign tissue in brain tumors with higher preciseness is the PET with the amino acid tracer *11c-methionin (MET) or 18-fluorethyltyrosin (FET).* Numerous studies have shown that the specificity of the MET-and FET-PET for marking tumor contours and for the differentiation relapse vs. radiation necrosis is higher compared with MRI. MET-PET is a clinical-established and in many studies evaluated investigation in diagnostics of gliomas. In comparative field test from CT, MRI, MET-PET and histological finding after stereotactic biopsy, MET-PET showed the highest exactness in the differentiation of tumor tissue. Also low-grade gliomas can be distinguished with this method with a sensitivity and specificity of about 80% from non-neoplastic alterations [3]. These qualities of the MET-PET can also be extrapolated to other well-known amino acid tracers: Langen et al. [4] showed that tumor expansion and intensity of tracer-uptake in MET-PET and IMT-SPECT correlates closely to each other in gliomas in spite of the differences in the methodology of the investigations. In the first clinical evaluation of FET-PET, the uptake of FET was compared with the uptake from MET in patients with intracerebral tumors. It was found that the uptake from FET and MET correlates closely to each other [5]. That applies to normal brain tissue as well as to tumor tissue (glioma and brain metastases). The essential advantages from FET compared to so far used amino acid tracers are the easy synthesis, the lack of metabolism in vivo as well as the favorable physical half-life of the used F-18 [5, 6, 7, 8].

An important advancement in integration of PET in therapy planning is the development of methods for co-registration. They allow an anatomical accordance of both investigations. As the calculation of the dose distribution is based on the attenuation information of CT and as, in many cases, the high resolution of the MRI is important for the illustration of the anatomy, a perfect co-registration PET/CT/MRI is essential in the high-precision radiotherapy of brain tumors [9].

First experiments to integrate the functional examinations in treatment planning have shown that IMT-SPECT compared to MRI can give additional information in regard to the tumor extension. In a comparison of tumor volumes of gliomas in MRI and SPECT with the amino acid tracer IMT was shown that in 23% an IMT-uptake was found outside of the in T2 hyperintense areas as an indication for tumor infiltration [10]. These findings were confirmed by other study groups in the MR-spectroscopy [11]. In operated patients, IMT-SPECT helps to distinguish residual tumor tissue from postoperative alterations (blood-brain-barrier-impairment, bleeding, oedema). Therefore, the integration of IMT-SPECT in treatment planning has an essential impact on the identification of the GTV: On the one hand, tumor volume is identified in an exacter way, on the other hand, brain areas which seem to be pathologic as a result of the operation or because of compression effects can be better spared. That fact can have an important consequence for the treatment planning, especially in dose escalation studies [12].

The importance of MET-PET for tumor volume definition in treatment planning was evaluated in comparison with MRI in 39 patients with malign gliomas after tumor resection: Only in 13% of cases, MET-PET volume accorded with gadolinium contrast uptake. In 74% the expansion of the MET-PET volume was larger than the Gduptaking region as an indicator for residual tumor. MET-PET positive tumor areas were found up to 4.5cm outside the contrast uptake in MRI. In 50% of patients, MET uptake was found outside of the in T2-weighted MRI-hyperintense areas [13]. In a prospective phase-II-study about stereotactic re-irradiation of patients with relapse of malignant gliomas, biologic imaging (MET-PET or IMT-SPECT) was used for target volume definition in 36 patients. These patients showed a significantly longer median survival compared with the group of patients, in which target volume was merely defined by CT and MRI [14].

Nuutien J et al. [15] integrated MET-PET in treatment planning of low grade gliomas and examined patients after radiotherapy in follow-up. With MET-PET, tumor areas could be distinguished from compression oedema. After radiotherapy a decrease of MET uptake was seen. Lee et al. [16] integrated MET-PET in treatment planning and showed that thereby tumor tissue can be better distinguished from healthy tissue.

Glucose-analogon F-18-fluordesoxyglucose (FDG) is used in diagnosis of extra cerebral malign tumors. In brain tumors, too, FGD-uptake correlates with histological grading and has a prognostic indication. But the high FDG uptake in normal grey matter results in a lower contrast between tumor and surrounding tissue. Low-grade tumors often appear just as activity defects. For this reason, FGD-PET can rarely give additional information for treatment planning: in a MRI/FDG-PET comparison field test, additional information to MRI was found only in one of 18 patients with high-grade brain tumors [17]. So despite the higher resolution, FDG-PET is inferior to PET for the definition of the tumor volume in brain tumors.

Menigiomas and glomus tumors show typically a high expression of somatostatin receptors. By absence of an intracerebral lesion in octreotid-scintigraphy, a meningioma or a glomus tumor is very improbable (sensitivity > 90%). As a positive finding in octreotid-scintigraphy is also possible for other lesions with impairment of the blood-brain-barrier, specifity of this investigation is low.

Meningiomas show a high MET and DOTATOC-PET-uptake. So by including the MET-PET, the interobservervariability decreased and the reproducibility of the target volume definition in planning of a stereotactic fractionated radiotherapy (SFRT) increased significantly [18,19]. Reason for the higher reproducibility was a better illustration of tumor infiltration in regions with physiologic contrast uptake in MRI, like for example, the cavernous sinus. It was revealed that by integration of MET - and DOTATOC-PET in the target volume definition, important areas like orbital cavitiy, optic nerves, sella turcica etc., could be better spared from the high dose area.

Biologic imaging leads to the so called “dose painting”

Molecular imaging like PET permits certain biological activities with a specific role in the course of the tumor response to be used as a target for an individual radiotherapy. Examples are hypoxia-, proliferation- and angiogenesis-imaging. Against the background of a biologic imaging, newest developments in radiation oncology can be described as follows: The dogma of a homogenous dose distribution inside the tumor is swaying. Innovative techniques in radiotherapy like, for example, the Intensity Modulated Radiation Therapy (IMRT) make it possible to constrain sub-volumes of a tumor (biologic target volume), which seems, based on imaging, to be very aggressive in matters of their biology, with a higher dose compared with the other tumor volume. The biologic imaging will therefore lead to an inhomogeneous dose distribution, the so called “dose painting”. Furthermore, biologic imaging can include therapy based alterations of the tumor biology (for example angiogenesis, re-oxygenesis) by replicated visualization during on-going fractionated radiotherapy, so therapy concept can be adapted to the current tumor biology. This hypothesis shall be verified in further clinical studies.

New methods for radiation treatment planning

Use of IMRT affords the treatment of irregular target volumes by “modulation” of the radiation dose inside the irradiated area. This modulation is achieved by segmentation of each irradiated area in multiple, differently figured subareas, which are irradiated with different dosage. The shaping of the segments is realized by the use of multileaf-collimators (80 to 120 computer guided lead leafs separately integrated in the irradiation device) which are already established in the conformal radiotherapy.

Multileaf-collimators also permit a dynamic adaption of the irradiated area during radiation treatment. By the static IMRT-method, each segment is successively irradiated (“step and shoot”). By the dynamic IMRT, the intensity-modulation happens by a leaf movement in different speed through irradiated areas during irradiation. New methods allow a continuous modulation of leafs and dose distribution during one rotation of the irradiation device (“volumetric modulated arc therapy”, VMAT or IMAT).

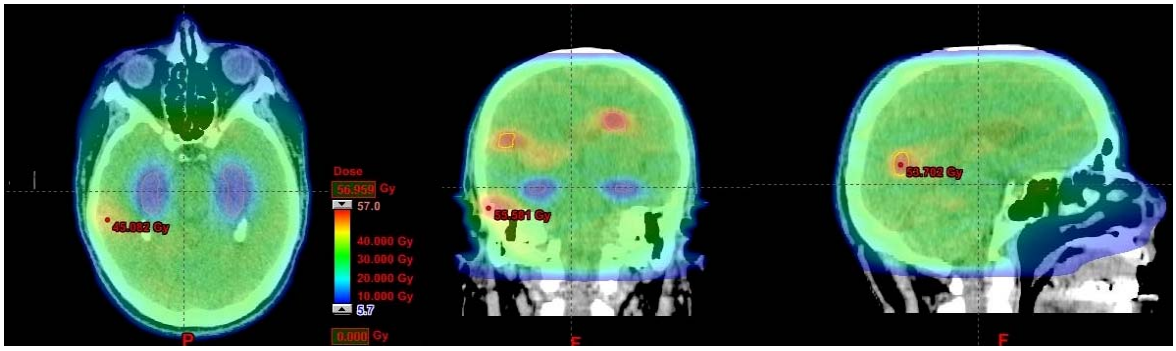
A special VMAT mode is tomotherapy. Thereby, a radiation source turns in a coil through 360°. The transversal fan beam is gated out with a dynamic leaf collimator. The favored dose distribution is realized, like in CT scan, by the combination of the rotation of the beam with the longitudinal movement of the radiation table. Before irradiation, the position of the patient can be verified with megavolt radiation in the form of a CT.

By the overlap of many segments, the favored dose distribution in the target volume and an adaption of the form of the irradiated area even to irregular tumor boundary is generated in the statistic as well as in the dynamic method. In the surrounding area of the target volume, an abrupt drop in dose is realized, whereby organs at risk and healthy tissue can be spared in an optimal way. Subareas inside the tumors, which appear to be very active in biologic imaging, can gain peak doses with the IMRT technique. This inhomogeneous dose distribution inside the target volume is called “dose painting”.

Techniques for an exact positioning of the patient for the radiation treatment

An essential precondition for the exact application of high radiation dosage to exactly defined target volumes is the reliable, reproducible positioning of the patient at the irradiation device. Regional incorrect irradiation can cause a reduction of the target volume dosage and concurrently a dose heightening in the field of the critical normal tissues. Moreover, a positioning variability demands an adding of safety margins to the target volume: Thereby the PTV is getting significantly bigger than the CTV. These safety margins include normal tissues, which are partially exposed to the prescribed (high) dose inside the target volume. Numerous methods are available by now for the reduction of such positioning variability.

Example: the implication of the new techniques for Radiotherapy of brain metastase



Patient with multiple brain metastases. Treatment with whole brain irradiation (green), simultaneous integrated boost to the metastases (red) and hippocampal sparing (blue). Neural stem cells are located in the hippocampal region, supporting lifelong neurogenesis. Avoidance of neural stem cells in hippocampus may reduce the neurotoxicity of whole brain irradiation, especially hippocampal functions like learning and memory. Mean dose to hippocampus is about 9Gy. However this hypothesis has to be demonstrated in clinical trials.

Radiosurgery / stereotactic fractionated radiotherapy

The term “stereotactic radiotherapy” denotes treatments and techniques, which permit with the aid of stereotactic coordinates, a geometrically precise beam application to an exact defined target volume and are characterized by an abrupt drop of dose to normal tissues [21]. The high preciseness of the irradiation is achieved by special stereotactic fixing, localization and positioning device. Stereotactic irradiation treatments can be passed percutaneously with gamma rays, ultrahard x-rays or interstitially with radioactive seeds. From all of these methods especially the percutaneous stereotactic radiotherapy at LINAC prevailed by its non-invasive character and high efficiency. The development of micro-micromultileaf-collimators for field forming permits an adaption of irradiated areas to irregular target volumes. Thereby, even irregular tumors can be irradiated homogenously and conformally.

The percutaneous stereotactic radiotherapy can be passed as one-time irradiation (radiosurgery, RS) or as stereotactic fractionated radiotherapy (SFRT). RS is approved for small, well limited lesions like brain metastases, small acusticneuromas, meningiomas or pituitary adenomas. RS also has a special impact for the treatment of ateriovenous malformations. RS can be passed at LINAC, at gamma knife (cobalt irradiation) or at cyber knife (small linear accelerator with robots). SFRT is indicated for lesions which include normal tissue (especially cranial nerves) inside the target volume

or which are localized close to organs at risk: bigger meningiomas, pituitary adenomas, craniopharyngiomas, acusticneuromas, and recurrent gliomas.

SFRT can be passed at LINAC or, as hypo-fractionated radiotherapy, at cyber knife (several higher single doses). The SFRT combines the geometrical preciseness of the stereotactic technique with the biological advantage of the dose fractionation. By fragmentation of the radiation dose in several small fractions at intervals of a few hours, enzymatic mechanisms inside the cells get active, which repair radiation injuries between two fractions. The so called "late responding normal tissue" like brain tissue shows a distinctive regeneration from sub lethal radiation injuries. So, this tissue can be spared with increasing fractionation of the radiation dose (lower single doses). In contrast, the so called "early responding tissue" shows, like many other tumors, only a low repair capability and thereby, only a lower fractionation effect. So, with SFRT, the healthy tissue can be better spared and the tumor tissue can be deleted.

The decision to treat a tumor with RS or SFRT shall be based on facts of radiobiological knowledge. Radiobiological qualities of healthy and tumor tissue, anatomic proportions, perfusion, combination with other treatments and specific concomitant diseases of the patient must be considered.

Beside the RS and the SFRT with conventional linear accelerators and the traditional gamma-knife-RS, the robotic RS with cyber knife has been established in the last few years. Thereby, the linear accelerator isn´t guided as hitherto by an isocentric gantry, but by a robotic arm with 6 degrees-of-freedom. By image-guided technology and computer based robotic, the system is able to track even moving target volumes and to irradiate in a high dosed conformal way. Intra-fractionated movements can be computer-based compensated. So the technology departs from ultimate principles of the stereotactic radiotherapy and belongs more to another new domain that is to say the image guided radiotherapy. The disadvantage of this method is the inhomogeneous dose distribution and the long treatment period (1-2h/fraction).

Image guided radiotherapy (IGRT)

The irradiation technique, which uses a higher preciseness of positioning by in the irradiation device integrated imaging, is called "image guided radiotherapy" (IGRT). With the IGRT, before, after, even during irradiation, an image is guided (x-ray, CT, ultrasound), that is compared with the imaging made for treatment planning with the aid of computer systems. Impreciseness of patient positioning is automatically corrected by computer guided movements of the treatment table. At LINAC, the IGRT is realized by an integrated CT, the so called cone-beam CT. Before application of the radiation, the CT made for treatment planning is compared to the CT made at the treatment table. If there is a deviation in the target-performance-comparison, the patient is according to that repositioned at the treatment table [22].

By imaging in the fields of tomotherapy, the radiation source rotates like in CT in an accordant circle. After generating and reconstruction of the images, the provided preciseness in the orientation of the radiation is realized by a comparison with the planning-CT. This is made to re-ascertain regularly the exact localization of an irradiated tumor.

Other radiation treatment modalities

Hadron therapy

Radiotherapy with hadrons is a special section in radio oncology. Hadrons, where protons, neutrons, pions and heavy ions belong to, have physical and biological qualities which differ from normal radiotherapy with photons and electrons. Photons and heavy ions are for example characterized by the so called bragg-peak - phenomenon. This inverted dose profile with the increase of the dose with increasing depth of penetration to the "bragg peak" (maximum) and the abrupt drop of dose behind the maximum, leads to a specific dose distribution, which permits a complete sparing of the healthy tissue behind the bragg peak.

Relative biological activity (RBA) of protons is similar to RBA of photons, whereas the heavy ions have a considerably higher RBA. In seldom tumors located in the base of the skull like chordomas and chondrosarcomas, there is a better local tumor control after radiotherapy with protons and heavy ions compared to photons. There is still few data for other tumor

entities. Role of hadrons in tumor treatment is still unclear. High technical effort is connected to high expense. The real clinical impact in the treatment of brain tumors is currently study-based investigated [23].

HDR - brachytherapy and intraoperative radiotherapy

Brachytherapy (gr. brachy close, brief) is an invasive form of radiotherapy. Thereby, one or multiple radiation sources are placed inside or in the very near of the tissue to be irradiated inside the body. A characteristic feature of brachytherapy is the fact that the radiation effect attacks only a very limited area around the radiation source. That's why the radiation exposure is strongly reduced for healthy and from radiation sources distant tissues. The accomplishment of a brachytherapy treatment needs few, but higher dosed irradiations, which lead to a shorter treatment time as other radio therapeutic methods. That can contribute to the fact that surviving tumor cells have less chance to part and to grow in the intervals between the single radio-therapeutic doses. In specialized centers, the high dose rate- (HDR) - brachytherapy for recurrent gliomas has been practiced. The precise application of radiation, after 3-dimensional CT-guided treatment planning, the maximal sparing of healthy tissue and the short treatment times are good arguments for this therapy. The results of this treatment shall be evaluated in further prospective multi-centric studies [24].

The intraoperative radiotherapy (IORT) describes another invasive irradiation method which attends the operation. The advantage of the IORT is the earlier radiation treatment with a higher single dose to an exact defined area. Like HDR-brachytherapy, the IORT is passed only in single specialized centers [25].

Conclusion

Radiotherapy of brain tumors has shown an enormous technical development in the last few years. In this chapter, we gave a résumé about the most important new treatment techniques. All of these methods have their pros and cons. Role of the radio oncologist is to find the best method for each tumor entity and tumor localization, for each oncological case, which treats the tumor in an optimal way and minimizes the risk of side effects. The decision to treat a brain tumor patient with radiotherapy should be interdisciplinary made in tumor boards.

References

[1] Brandsma D., Stalpers L., Taal W. et al. (2008) Clinical features, mechanisms, and management of pseudoprogression in malignant gliomas. Lancet Oncol. 9(5):453-61. http://dx.doi.org/10.1016/S1470-2045(08)70125-6

[2] Brandsma D., van den Bent M.J. (2009) Pseudoprogression and pseudoresponse in the treatment of gliomas. Curr Opin Neurol. 2009 Sep 16.

[3] Herholz, K., Holzer T., Bauer B. et al. (1998). 11C-methionine PET for differential diagnosis of low-grade gliomas. Neurology 50(5):1316-22. PMid:9595980

[4] Langen KJ, Tatsch K, Grosu AL, Jacobs AH, Weckesser M,Sabri O: Diagnostik von Hirntumoren mit radioaktiv markierten Aminosäuren. Deutsches Ärzteblatt 2008;105(4):55-61

[5] Grosu, A. L., Astner S.T., Riedel E. et al. (2010). O-(2-(18F) Fluorethyl)-L-tyrosine and L-(Methyl-11C)-Methionine PET for Determination of Tumor Extension in Gliomas and Brain Metastases.

[6] Weber, W. A., Wester H.J., Grosu A.L. et al. (2000). O-(2-[18F] fluoroethyl)-L-tyrosine and L-[methyl-11C] methionine uptake in brain tumors: initial results of a comparative study. Eur J Nucl Med 27(5):542-49. http://dx.doi.org/10.1007/s002590050541

[7] Pauleit D., Floeth F., Tellmann L. et al. (2004). Comparison of O-(2-18F-fluoroethyl) L-tyrosine PET and 3-123I-iodo-alpha-methyl-L-tyrosine SPECT in brain tumors. J Nucl Med 45(3):374-81. PMid:15001676

[8] Popperl G., Gotz C., Rachinger W. et al. (2004). Value of O-(2-[18F] fluoroethyl) - L-tyrosine PET for the diagnosis of recurrent glioma. Eur J Nucl Med Mol Imaging 31(11):1464-1470. PMid:15248032 http://dx.doi.org/10.1007/s00259-004-1590-1

[9] Grosu A.L., Lachner R., Wiedenmann N. et al. (2003). Validation of a method for automatic image fusion (BrainLAB System) of CT data and 11C-methionine-PET data for stereotactic radiotherapy using a LINAC: first clinical experience. Int J Radiat Oncol Biol Phys 56(5):1450-63. http://dx.doi.org/10.1016/S0360-3016(03)00279-7

[10] Grosu A.L., Weber W.A., Feldmann H.J. et al. (2000). First experience with I-123alpha-methyl-tyrosine spect in the 3-D radiation treatment planning of brain gliomas. Int J Radiat Oncol Biol Phys 47(2):517-26. http://dx.doi.org/10.1016/S0360-3016(00)00423-5

[11] Pirzkall A., Li X., Oh J. et al. (2004) 3D MRSI for resected high-grade gliomas before RT: tumor extent according to metabolic activity in relation to MRI. Int J Radiat Oncol Biol Phys. 1;59(1):126-37.

[12] Grosu A.L., Feldmann H.J., Dick S. et al. (2002) IMT SPECT OP Implications of IMTSPECT for postoperative radiotherapy planning in patients with gliomas. Int J Radiat Oncol Biol Phys. 1;54(3):842-54

[13] Grosu, A.L., Weber W.A., Riedel E., et al. (2005). L-(methyl-11C) methionine positron emission tomography for target delineation in resected high-grade gliomas before radiotherapy. Int J Radiat Oncol Biol Phys 63(1):64-74. PMid:16111573 http://dx.doi.org/10.1016/j.ijrobp.2005.01.045

[14] Grosu, A.L., Weber W.A., Franz M. et al. (2005a). Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys 63(2):511-19. PMid:16168843 http://dx.doi.org/10.1016/j.ijrobp.2005.01.056

[15] Nuutinen, J., Sonninen P., Lehikoinen P. et al. (2000). Radiotherapy treatment planning and long-term follow-up with [(11) C] methionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys 48(1):43-52. http://dx.doi.org/10.1016/S0360-3016(00)00604-0

[16] Lee I.H., Piert M., Gomez-Hassan D. et al. (2009) Association of 11C-methionine PET uptake with site of failure after concurrent temozolomide and radiation for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys. 1;73(2):479-85.

[17] Gross M.W., Weber W.A., Feldmann H.J. et al. (1998) the value of F-18fluorodeoxyglucose PET for the 3-D radiation treatment planning of malignant gliomas. Int J Radiat Oncol Biol Phys.15;41(5):989-995.

[18] Grosu A.L., Weber W.A., Astner S. et al. (2006) 11C-Methionine PET improves the target volume delineation of meningiomas treated with stereotactic fractionated radiotherapy. Int J Rad Oncol Biol Phys 66:339-344. PMid:16765533 http://dx.doi.org/10.1016/j.ijrobp.2006.02.047

[19] Astner S.T., Dobrei-Ciuchendea M., Essler M. et al. (2008) Effect of 11C-methioninepositron emission tomography on gross tumor volume delineation in stereotactic radiotherapy of skull base meningiomas. Int J Radiat Oncol Biol Phys 15;72(4):11617.

[20] Bortfeld T., Thieke C. (2006) Optomization of Treatment Plans, Inverse Planning. In Schlegel W., Bortfeld T., Grosu A.L. (Eds.) New Technologies in Radiation Oncology, Springer:207-20.

[21] Grosu A.L., Kneschaurek P., Schlegel W. (2006) Stereotactic Radiotherapy/Radiosurgery. In Schlegel W, Bortfeld T, Grosu AL (Eds) New Technologies in Radiation Oncology, Springer:267-76.

[22] Yan D. (2006) Image-Guided/Adaptive Radiotherapy. In Schlegel W., Bortfeld T., Grosu A.L. (Eds.) New Technologies in Radiation Oncology, Springer:321-36.

[23] Phase i study evaluating the treatment of patients with hepatocellular carcinoma (HCC) with carbon ion radiotherapy: the PROMETHEUS-01 trial; Combs SE, Habermehl D, Ganten T, Schmidt J, Edler L, Burkholder I, Jäkel O, Haberer T, Debus J., BMC Cancer. 2011 Feb 12;11:67. PMid: 21314962

[24] Tselis N., Kolotas C., Birn G. et al. (2007) CT-guided interstitial HDR brachytherapy for recurrent glioblastoma multiforme. Long-term results. Strahlenther Onkol;183(10):563-70. PMid:17896088 http://dx.doi.org/10.1007/s00066-007-1721-2

[25] Schueller P., Micke O., Palkovic S. et al. (2005) 12 years' experience with intraoperative radiotherapy (IORT) of malignant gliomas. Strahlenther Onkol;181(8):500-506. PMid:16044217 http://dx.doi.org/10.1007/s00066-005-1354-2