

metastasize outside de CNS. The retinoblastoma (Rb) tumor suppressor gene is a negative cell-cycle regulator. Hypophosphorylated Rb protein (pRb) binds and inactivates the E2F1 transcription factor regulator of DNA synthesis. However, mitogens, trigger cyclins D transcription, and binding to cyclin-dependent kinases (CDKs) 4 and 6, which initiate pRb phosphorylation, completed by cyclin E-CDK2.

Hyperphosphorylated pRb loss growth suppression function, releasing E2F1, leading to DNA synthesis and cell-cycle progression. The p53 gene plays a central role in the stress response to DNA damage and hyperproliferative signals, to prevent the growth and survival of potentially malignant cells. Activation of p53 may induce G1/S cell cycle arrest to allow DNA repair, or in case DNA is irreversibly damaged, can induce apoptosis. p53 & Rb pathways were investigated by Immunohistochemistry detection of (p14/ARF, p53, p21/WAF1, HDM2), (Rb, E2F1, Cyclins D1, D3 and E, CDK4, p16/INKa) protein expression, in 18 MHPC's (11 primary, 4 of them recurrent in 1, 1, 2 and 4 occasions). Double Immunofluorescence (DIF) staining and Laser Scanning Confocal Microscopy (LSCM) was used to address co-localization and molecular interactions. Simultaneous p53 and wild type p53 trans-activated genes (p21/WAF, HDM2) expression occur in all cases. This argues against p53 mutation. HDM2 over expression was observed in 10 cases (55.5%). DIF staining and LSCM displayed HDM2 and p53 co-localization.

This strongly suggests that HDM2 binds and inactivates p53. Rb protein expression was low in 13 cases, negative in four and over expressed in one. Over expression of E2F1 (10 cases), Cyclin E (7 cases), CDK4 (5 cases), Cyclin D3 (2 cases) and Cyclin D1 (1 case) was observed. Low Rb expression and E2F1 over expression suggest impairment of Rb function. Rb and E2F1 co-localization was very weak or negative by DIF&LSCM. This argues that Rb is not binding and inactivating E2F1 and not acting as a suppressor. Moreover, HDM2 and E2F1 co-localization was frequently observed. This strongly suggests that HDM2 binds and activates E2F1.

Publication

Central nervous system

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PUBLICATION

Tomotherapeutic intensity-modulated radiosurgery: improving dose gradients and maximum dose after inverse optimization using ActiveRx

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Intensity-modulated radiosurgery (IMRS) for brain metastases and AVM using the Nomos Peacock IMRT system has been delivered in >150 cases in our institution over the last 4 years. A new software tool provided within the Corvus planning software allows for post inverse planning re-optimization and individualization of the dose distribution. We analyzed this tool with respect to increasing the steepness of the dose gradient and dose inhomogeneity while maintaining conformity.

Fifteen radiosurgery plans for solitary brain metastases that were clinically delivered during the last two months were analyzed. All plans were copied and ActiveRX, a tool available during plan review, was opened. The toolset in ActiveRX includes an eraser, a pencil to redefine isodose lines and a drag and drop tool, allowing reshaping of isodose lines. To assess changes in the steepness of the dose gradient and dose homogeneity, the 100%, 90%, 50% and 25% isodose volume, the volume of the target, maximum dose and mean dose to the target were sampled.

Target volumes ranged from 0.6 to 14.1 cm³ (mean/median 3.9/1.8 cm³). Mean RTOG conformity index (CI) of plans delivered was 1.23±0.31, mean homogeneity index (HI) was 115±5%. Using ActiveRX, the mean CI was slightly improved to 1.14±0.1, with associated increase in HI to 141±10%. The average respective Ian Paddick CI for the 100%, 90% 50% and 25% isodose lines were 0.79 vs.0.83, 0.44 vs. 0.59, 0.12 vs. 0.19, and 0.04 vs. 0.07, with significant improvements using ActiveRX post-optimization.

A post inverse planning optimization tool for IMRS plans allowed for statistically significant improvements in the steepness of the dose gradient, and increased maximum and mean target doses compared to clinically delivered plans that were already considered excellent. Gains were especially pronounced in the reduction of normal brain tissue included into the 90%, and 50% isodose lines. We have since made this process part of the clinical routine for all cranial IMRS procedures.

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PUBLICATION

The influence of dose and target volume on results of radiosurgery for brain arteriovenous malformation

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Background: Stereotactic radiotherapy is non-invasive and effective method of AVM treatment. Tumor volume and delivered dose are very important factors limiting effectiveness of radiosurgery.

Material and methods: The retrospective analysis of stereotactic radiotherapy effectiveness for arteriovenous malformation (AVM) was done. 47 cases (27 male 20 female) of brain AVM treated with radiosurgery were analyzed. Mean age was 41. The most frequent tumour location was frontal and parietal lobe. Mean time of symptoms was 54 months. 14 patients were after neurosurgery (embolization). 90% of patients were in good performance status (ZUBROD 0 or 1). 12 patients had significant neurological symptoms. Tumor volume varied from 0.06 to 101 cm (mean 4.6). Mean total dose was 15 Gy and ranged from 7 to 20 Gy. Mean of irradiated fields number was 9. In 42 cases conformal and in 8 cases intensively modulated radiosurgery were used. Tolerance of treatment was acceptable (only 4 patients had side effects). Median follow up varied from 1.3 to 47 months (mean 14.7 Gy). Tumor size and malformation of blood flows based MRI, CT and angioMRI images and neurological status 6, 12, 24 months after RT were assessed. Time to malformed blood vessels obliteration was measured. Correlations between particular assessed parameters were checked using Spearman test. Influence of total dose and tumor volume on treatment results was analyzed using logistic regression test.

Results: The complete tumor regressions (CR) evaluated using MR or CT scans were observed within 6 months in 27% of patients, in 31% within 12 months and in 50% of patients within 24 months then radiotherapy completion. Partial regressions (PR) were observed in 41% of patients 6 months after treatment, in 21% 12 months and in 20% 24 months after radiotherapy. Mean time to partial AVM vessels obliteration was 7.8 months and mean time to complete vessels obliteration was 10.8 months. Overall response rate (CR+PR) was 53%. Spearman analysis showed only negative correlation between tumor volume and MR or CT based tumor regression 3 months after RT ($p=0.03$, $R=-0.35$). Logistic regression revealed that only total dose has negative influence on partial regression ($p=0.008$), target volume does not influence on PR. Analysis in subgroups proved this influence only for patients who delivered total dose less than 16 Gy. Further logistit regression analysis showed that neither target volume nor total dose has influence on tumor CR and overall regression.

Conclusions: Stereotactic radiosurgery is safe and non invasive modality of AVM treatment, giving 53% of overall responses. Target volume has no influence on probability of tumor regression but delivered dose influences on tumor partial regression.

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PUBLICATION

Postoperative radiotherapy and chemotherapy in the management of oligodendroglioma: single institutional review of 88 patients

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Background: We retrospectively evaluate the prognostic factors affecting the local control, survival and the potential role of chemotherapy in the management of patients with oligodendroglioma.

Material and methods: The medical records of 88 patients treated by postoperative external beam radiotherapy ± chemotherapy at our institution between December 1993 and December 2002 were analyzed. Nine patients (10%) were treated with an accelerated fractionation scheme, while 79 patients were treated with conventional doses. The median RT dose was 54.8±2.58 Gy for low-grade tumors, and 58.7±2.46 Gy for high-grade tumors. PCV chemotherapy regimen was given to 18 patients; temozolamide was administered in 3 patients. Chemotherapy was not given concomitantly in any patients.

Results: The median follow-up was 56 months (range 7–134 months). The 5-year overall and progression-free survival rates for entire group were 86% and 79%, respectively. Patients with epilepsy at presentation had better 5-year overall survival (93% vs. 74%, $p=0.04$). High grade tumors had significantly lower overall survival rate. Age, presence of motor deficit at diagnosis and histological grade were found have a significant impact on progression-free survival. The 5-year overall and progression free survival rates of patients with high-grade tumors were 69%, 51% and 74%, 68% for chemotherapy and nochemotherapy group, respectively ($p=0.9$ for OS, $p=0.3$ for PFS). In multivariate analysis no significant factor affecting the overall survival and progression-free survival was found.

Conclusion: Chemotherapy given after postoperative radiotherapy in patients with oligodendroglioma did not improve survival in this retrospective study.

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PUBLICATION

Analysis of prognostic factors in patients with glioblastoma multiforme treated with postoperative radiotherapy

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Purpose: To evaluate prognostic factors of patients with Glioblastoma multiforme (GBM) treated with postoperative radiotherapy (RT).

Materials and methods: Between October 1995 and December 2003, 80 patients with newly diagnosed GBM were treated with postoperative RT at our department. Patients were assigned to RPA groups. We also evaluated several potential prognostic factors for survival. The influence of various factors of age, sex, Karnofsky performance status (KPS), histology, a history of seizure at diagnosis, type of surgery, RT dose, median waiting time from operation to RT, median duration of RT, duration of symptoms, presence of chemotherapy, initial tumor size, postoperative tumor size, neurologic status of preoperative, postoperative and after RT, family history of cancer and RPA groups on overall survival were studied. The Kaplan-Meier method, Log-rank test and the Cox proportional hazard model were used for statistical analysis.

Results: All patients evaluated in April 2005. Median follow-up was 8 months (1–37 months) and 89 patients died at analysis time. Median age was 55 years (20–73 years) with 49 male and 31 female patients. Surgical treatment consisted of biopsy, subtotal resection and total resection of 16, 39 and 25 patients, respectively. All patients had received external beam radiotherapy with a median dose of 60 Gy (22–66 Gy). In 2 cases (2.5%) the tumor was multicentric. The median waiting time from operation to RT was 20 days (1–54 days) and the median duration of RT was 42 days (15–71 days). A total of 33 patients received adjuvant or concurrent chemotherapy with RT. The overall median survival was 8 months (1–37 months) for the total group and 15, 8, 9 and 3 months for RPA group III (n = 12), IV (n = 35), V (n = 29) and VI (n = 4), respectively. The 1, 2 and 3 year overall survival rate were 31%, 5% and 2%, respectively. The following parameters were significantly associated with prolonged survival:

1. KPS of 80 or more (10 and 4 months, $P < 0.001$)
2. total tumor resection (13 and 7 months, $P < 0.001$)
3. total dose of RT (< 60 Gy vs > 60 Gy; 3 and 9 months, $P < 0.001$)
4. initial tumor size (≤ 4 vs > 4 cm; 9 and 8 months, $P < 0.001$)
5. absence of neurologic deficit after surgery (10 and 6 months, $p < 0.001$)
6. absence of neurologic deficit after RT (11 and 5 months, $p < 0.001$) and RPA groups ($p < 0.05$).

Conclusion: Glioblastoma multiforme remains an important cause of morbidity and mortality from intracranial tumors. Karnofsky performance status, total tumor resection, total dose of RT, initial tumor size, absence of neurologic deficit and RPA groups are prognostic factors for predicting survival of GBM patients.

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PUBLICATION

Radiosensitized treatment of different brain tumors with hematoporphyrin derivative

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Background: While primary malignant brain tumors account for only 2% of all adult cancers, these neoplasms cause a high amount of cancer-related deaths. The incidence of primary brain tumors is increasing, so the emergence of novel treatment methods for these tumors has led to heightened interest. High level of porphyrins is noticed in glioma tissue, therefore sensitized gliomas treatment is hopeful. Our hypothesis was that the some of the rays who can provide ionizing radiation (x-rays and/or gamma rays) could activate some of hematoporphyrin derivatives (HpD). To prove it, we have performed experiments on mice and rats. A favourable outcome of our animal experimental study has encouraged us to utilize radiosensitized treatment (RST) in Lithuanian Oncology Center in 1989. The purpose of this work was to investigate and to enlarge the possibilities of sensitized brain tumors treatment using some HpD as radiosensitizer.

Materials and methods: Since 1998 03 the total of 89 patients with advanced primary or metastatic brain tumors underwent RST as palliation. There were 58 patients with primary malignant tumors and 27 patients with solitary metastatic brain tumors (16 patients) or with tumors, which were grown into the brain from the surrounding tissue (11 patients). There were 4 patients with primary benign tumors too. Tumors

were irradiated with gamma rays 2 Gy at a time from radioactive ⁶⁰Co 24, 48 and 72 h after injection i.v. of the HpD (the full dose of the course was 6 Gy). 23 patients underwent a single course of RST, for the rest RST was repeated. CT- and/or MRI-examination was provided for all patients before the treatment and 1–1.5 mo. after each RST course.

Results: As the immediate result of RST of malignant brain tumors, 31 malignancies (in 14 patients) fully disappeared. However the recurrent disease was noticed in 4 of them after 49; 37; 24 and 6 mo. The significant response – the regression of tumor and remission of the disease for more than 6 mo. – was observed in 24 patients. Partial response was noticed in 25 patients. For the rest patients the treatment was ineffective. RST was ineffective for all patients with benign brain tumors.

Conclusions: RST is a new and effective method of treatment in malignant brain tumors both primary and metastatic. The effectiveness of RST depends on the morphological type of tumor.

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PUBLICATION

Therapeutic results in patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) receiving postoperative radiotherapy and concomitant temozolomide

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Background: We retrospectively evaluate our therapeutic results in patients with anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) receiving postoperative radiotherapy and concomitant temozolomide.

Materials and method: The medical records of 32 patients treated by postoperative external beam radiotherapy (RT) and concomitant temozolomide chemotherapy at our institution were analyzed. Karnofsky performance score (KPS) was above 70 in all patients. There were 10 female and 22 male patients with a median age of 49 years (range, 21–53 years). Histopathology was GBM in 25 and AA in 7 patients. Subtotal excision was performed in 19 and gross total excision in 12 patients. Three patients were treated with an accelerated fractionation scheme (1.5 Gy bid to a total dose of 45 Gy), while 29 patients were treated with conventional scheme (2 Gy daily to a total dose of 60 Gy). Initial radiotherapy portals included primary tumor volume plus 3 cm, and boost volume included primary tumor plus 1 cm. Localization was performed after 40.5 Gy for accelerated scheme and after 40 Gy for conventional scheme. Temozolomide was given in 100 mg/m² doses (PO once daily, max. dose 200 mg), during the first and the third week of RT course in 17 patients. Since this dosage was well tolerated, we increased dosage to 150 mg/m² (PO once daily, max. dose 300 mg) in last 15 patients. Informed consent was obtained from all patients before the start of therapy.

Results: The median follow-up was 10 months (range 3–17 months). Nineteen patients had either no evidence of disease or stable disease, while progression was observed in 7 patients at last follow-up. Six patients died of disease. The median overall survival was 15 months (17 months for AA, and 14 months for GBM, $p = 0.06$). Patients with gross total excision had better overall survival than patients with subtotal excision (17 months vs. 13 months, $p = 0.05$) in univariate analyses. Gender, age, KPS, type of surgery, grade, and RT scheme were analyzed as prognostic factors in multivariate analysis, and no significant factor affecting the overall survival was found. Emesis was the predominant toxicity during treatment observed in 9 patients (28%). Skin toxicity due to drug reaction were seen in 2 patients. But both received phenytoin with temozolomide. No other serious acute and late toxicity was noted due to either RT or temozolomide.

Discussion: Postoperative radiotherapy and concomitant temozolomide seems to be an effective and safe treatment regimen for patients with AA and GBM.

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PUBLICATION

Temozolomide in the treatment of high grade gliomas

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Purpose: to present the results obtained in treatment of primary high grade gliomas with postoperative radiotherapy and chemotherapy with Temozolomide, the toxicity and the compliance to treatment.

Material and methods: We treated 61 patients between 1999–2004. The median age was 41 years (10 and 64 years old). Histology: 30 patients with glioblastoma multiforme, 23 patients with anaplastic astrocytoma and 8 patients with anaplastic oligoastrocytoma. The standard treatment was surgery followed by radiotherapy. There were 39 patients with macroscopic total resection and 22 with partial resection. Postoperative radiotherapy consisted in focal irradiation in daily fractions of 1.8–2 Gy/5 days per week