of signal transduction inhibitors which lead to tumor radiosensitization such as the EGFR inhibitor Iressa®, the Ras processing inhibitor FTI L744,832®, is associated with a decrease in the active form of AKT, direct pharmacological inhibition of the PI3K/AKT pathway by LY291002 and wortmanin cause radiosensitization. Therefore, pharmacological targeting of the PI3K/AKT pathway is a promising novel strategy to improve tumor response to ionizing irradiation.

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Modulators of apoptotic signaling

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In order to increase the efficacy of ionizing radiation or to reduce radiation mediated side effects research centers for translational radiation oncology head for a specific modulation of defined cellular death pathways. In this regard, several signaling systems proved to be of high potential value. It has previously been shown that apoptotic pathways induced by ionizing radiation are distinct from pathways triggered by death ligands (e.g.TRAIL). The combination of both was highly efficient in vitro and preclinical mouse models. However, several aspects of normal tissue toxicity have not been solved and no phase I data are available yet. Thus, up to now the use of TRAIL is limited to experimental settings. A second approach which is currently tested in a phase I trial is based on the observation that synthetic phospholipid derivatives strongly enhance apoptotic effects by modulating the balance between the mitogenic, antiapoptotic MAPK and phosphatidylinositol 3'-kinase (PI3K)/Akt, and the proapoptotic JNK signaling pathways. Furthermore, others provided evidence that an inhibition of anti-apoptotic signals by mitogenic signals increases radiation responses. In this context, controversial data are available regarding the influence of a pharmacological abrogation of MEK1, Erk1/2 signaling on apoptosis sensitivity. However, inhibition of the PI3K/Akt survival pathway using compounds like the PKC inhibitor PKC412 was shown to induce apoptosis or to increase the apoptosis sensitivity of tumor cells. Therefore, these drugs may be used alone or in combination with radiation in order to increase tumor control. Several other drugs including COX-2 inhibitors, betulinic acid and proteasome inhibitors were shown to interact with apoptosis signal transduction. Again, most of the drugs have not been tested in combination with radiation in vivo or – in the case of COX-2 inhibitors – exert pleiotropic effects. Although the examples presented above cannot be considered to reflect all available strategies, it becomes clear that several promising approaches targeting defined cell death pathways have been developed and entered clinical trials. The use of synthetic phospholipid derivatives in a phase I trial is one of the first important examples proving that basic research in radiation biology finally guides the development of new treatment strategies. This and other approaches will increase tumor control rates and reduce side effects in the future.

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Molecular determinants of glioma biology

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We have been studying a series of 190 astrocytic gliomas (136 glioblastomas (GB), 39 anaplastic astrocytomas (AA) and 15 astrocytomas (A)) for abnormalities of genes in the RB1 pathway (CDKN2A, CDKN2B, CDK4 and RB1), the p53 pathway (p14ARF, MDM2, and TP53), as well as PTEN and EGFR. A main finding was that 67% of A and AA had no wild-type TP53 or one mutated allele with a wild type allele. These were the main findings A and AA. Only 29% of the GB had no wild type TP53 and an additional 6% had one mutated allele. Loss of wild type p14ARF occurred in 38% of GBs and a further 8% had amplification and overexpression of MDM2. Thus 76% of GB (103/136), 72% of AA (28/39) and 67% of A (10/15) had a deregulated p53 pathway - almost a prerequisite for astrocytic tumors. All A had at least one wild type RB1 gene and no other abnormalities of this pathway. Abnormalities of the RB1 pathway occurred in 21% AA and 67% GB either by mutation/loss/ homozygous deletion of RB1, CDKN2A and CDKN2B, or amplification of CDK4, indicating that disruption of the RB1 pathway is involved in astrocytic tumour progression. Amplification of the EGFR gene was not observed in A, was unusual in AA (8%) but common in GB (33%). Loss of wild type PTEN occurred in one AA (3%) but in 47% of GB. Both EGFR amplification and loss of wild type PTEN were found with all combinations of the other genetic abnormalities. Survival of patients with GB is typically 11 to 12 months. We studied whether any of the genetic factors examined were related to survival in GBs. Abnormalities in any of the four genes (CDKN2A, CDKN2B, RB1, CDK4) coding for components of the Rb1 pathway were associated with shorter survival (p=0.002). When combined with loss of wild-type PTEN the association was stronger (p

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What next in low grade glioma therapy

Abstract not received.

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Does radiotherapy matter?

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Radiotherapy (RT) remains the principal treatment modality in patients with malignant glioma. Conventional treatment to 60 Gy provides median survival benefit of approximately 6 months with no further advantage for higher doses. RT should be tailored to prognosis with radical treatment reserved for favourable prognosis patients; those with adverse prognostic features (defined by age and performance status) should receive palliative treatment. Attempts at improving the results of RT have concentrated on altered dose and fractionation (hyperfractionation and/or acceleration), the use of modifiers of radiation response and particle irradiation. Most have shown little benefit in single arm or randomised studies. High dose localised irradiation in the form of brachytherapy or stereotactic radiosurgery/radiotherapy boost have also failed to demonstrate prolongation of survival while associated with increased toxicity. Present research strategies concentrate on biological methods to overcome tumour hypoxia, on combined chemoradiotherapy approaches and on the use of biological modifiers, which may in association with radiation improve therapeutic ratio. New agents under evaluation include modifiers of EGFR signalling pathway, COX 2 inhibitors, modifiers of Ras signalling pathway and angiogenesis inhibitors. Radiotherapy remains the most effective primary treatment modality in patients with malignant glioma. New approaches to modification of radiotherapy have a real chance to demonstrate improved therapeutic ratio over RT alone. Before introduction into clinical practice they need robust preclinical and clinical testing.

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Current status of malignant glioma chemotherapy - hype or hope?

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Brain tumors are among the most debilitating diseases. Treatment options are limited to surgery and radiation, the role of chemotherapy has been marginal. Nitrosourea-based chemotherapy has shown activity in selected patients, but failed to show a benefit as adjuvant therapy for malignant glioma in a large randomized trial. Higher response rates to PCV-chemotherapy have been demonstrated for oligodendroglioma, in particular when associated with deletions on chromosomes 1p and 19q. Recently temozolomide (TMZ), a novel alkylating agent has been approved. The low response rates of only 5-8% in glioblastoma (higher in anaplastic astrocytoma) and the absence of phase III data have cast doubts whether TMZ offers a clinically relevant benefit over older alkylating agents. Some benefit may simply be derived by the closer follow-up and better supportive care in patients receiving chemotherapy. More intensive TMZ schedules are being explored. Continuous administration of alkylating agents will deplete the cells of the DNA repair enzyme O6-alkyltransferase (AGT), and may thus have a theoretical advantage over the intermittent schedules. No comparative data are available. Combining X-irradiation with TMZ has been shown to be at least additive in vitro in some glioblastoma cell lines. Using chemotherapy with intrinsic activity immediately after diagnosis together with radiotherapy may allow eliminating microscopic infiltrating disease early in the disease course. Concomitant administration of chemoradiotherapy may increase the radiosensitivity. In a phase II trial we treated 64 patients with newly diagnosed glioblastoma multiforme with TMZ and concomitant radiotherapy. At a median follow-up of now over 3 years the median survival of 14.3 mo (95% c.i. 10.4-18.3) and in particular the 2-year survival of 28% (17-39%) are promising for this poor-prognosis group of patients. A large international randomized trial conducted by the EORTC and the NCI Canada has accrued over 550 patients. Conclusive resuts are expected in early 2004. Insights into gene expression and signaling pathways have

allowed identifying new and specific treatment targets for malignant glioma. Trials using new agents blocking EGFR, PDGF and integrins are underway and some encouraging responses have been observed. The challenge remains to identify the patients who are most likely to benefit from new treatment approaches and integration of the novel agents into the existing multimodality treatments.

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Investigational therapies in glioma - from drugs to biological modifiers and back

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Progress in the management of high grade gliomas has been modest during the past three decades. Although surgery and radiation provide clear benefits, additional improvement in survival from these modalities is unlikely. Chemotherapy currently adds little to outcome. Clinical research using novel agents and approaches are needed as these tumors remain rapidly progressive and universally fatal. A wide range of new compounds and delivery methods are now available for study. The efficacy of novel cytotoxic agents can be evaluated using small numbers of carefully selected patients with previously untreated glioblastoma multiforme. If responses are not seen in this patient population, an agent can be declared inactive and others can be studied. The efficacy of radioenhancers, antiangiogenesis and other non-cytotoxic agents can be assessed by administering them with radiation to 54 patients with newly diagnosed glioblastoma multiforme using survival as the endpoint. This will provide sufficient statistical information to make reasonable decisions regarding the development of these agents. Recent discoveries of interactions between enzyme inducing antiepileptic drugs and the pharmacology of biologic and chemotherapy agents have had a profound effect on clinical brain tumor research. Studies are now moving from measuring concentrations of novel agents in blood to measurements within the brain tumor using microdialysis catheters in patients with glioblastomas. Finally, a variety of novel locally administered therapies using convection or investigational devices to deliver interstitial radiation, chemotherapy, and biologics are entering trials. These will facilitate the development of combination therapies in patients with locally recurrent tumors. Each of these concepts and approaches will be presented using examples from the NABTT CNS Consortium to highlight the expanding potential for innovative clinical research in patients with high grade gliomas.

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Epidemiology (including HPV)

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Cervical cancer epidemiology and the causal association between Human Papillomavirus infections and cervical cancer. On several occasions, estimates of the burden of Human Papillomavirus (HPV) infections and of the closely associated cervical lesions have been produced. Data on invasive cervical cancer extrapolated to the existing population indicate for Europe some 65.000 new cases per year and an age-standard rate of 13 new cases per 100.000 per year. Data on genital HPV-DNA prevalence in representative samples of populations in different countries are limited. Typically the proportions of HPV-DNA carriers have been placed in the 15-40% range in the young, sexually active, age groups and between 3-10% range in the 35 and above age groups. Prevalence in the male external genitals is only available for a few countries and the evidence suggests that may be roughly similar to the prevalence in women.

The association of HPV and cervical cancer. State-of-the art amplification techniques have unequivocally shown that in adequate specimens of cervical cancer HPV-DNA can be detected in 90 to 100% of the cases as compared to a prevalence of some 5-20% from cervical specimens of women identified as suitable epidemiological controls. Detailed investigations of the few cervical cancer specimens that appear as HPV DNA negatives in most series has been occasionally conducted and the results strongly suggest that these are largely false negatives. As a consequence, the claim has been made that this is the first *necessary cause* of a human cancer ever identified, providing a strong rationale for the use of HPV tests in screening programs and for the development of HPV vaccines.

Risk estimates from IARC's case control studies. The pool of IARC studies is large enough to provide, for the first time, type specific risk estimates for 18 types. The adjusted Odds Ratios (OR) for HPV DNA detection (the factor by which the reference risk of cervical cancer is multiplied if HPV DNA is detected) was OR any single type = 172.6 (95%CI: 122.2-243.7). Type specific risk estimates were as follows: HPV 16: OR= 435; HPV 18: OR= 248; HPV 45: OR= 198; HPV 31: OR= 124; HPV 33: OR=374; HPV 35: OR=74; HPV51: OR= 67; HPV 52: OR= 200; HPV 58: OR= 115; HPV 59: OR= 419. The risk for any given high-risk type was not statistically different from the risk reported for HPV 16. The risk related to the presence of multiple HPV types in the specimen is no different from the risk linked to a single HPV type. The standard estimates of the attributable fraction (AF%) -the proportion of disease that is related to HPV DNA- derived from these and most other studies range from 90 to 98%. The practical conclusions from these analyses strongly indicates that, under current evidence, group testing of clinical specimens for a cocktail of high risk types should be sufficient for screening and patient management. One of such tests, Hybrid Capture 2 (HC2), is commercially available and progressively introduced in clinical practice. Individual typing remains necessary in research settings and for studies evaluating therapeutic or preventive type-specific HPV vaccines.

Conclusion: The association between HPV exposures and cervical cancer has been recognized as causal in nature and furthermore as a necessary cause. This implies that in the absence of the persistent viral presence, cervical cancer is not expected to develop. This milestone recognition is reshaping the preventive scenario, in the screening and vaccination fields

Recommended reading:

[1] Bosch FX, Lorincz A, Muñoz N, Meijer CJLM, Shah KV. *The causal relation between human papillomavirus and cervical cancer.* J Clin Pathol 2002, 55(4): 244-265

[2] Muñoz N, Bosch FX, de Sanjosé S, Herrero R, Castellsagué X, Shah KV, Snijders PJF, Meijer CJLM, for the International Agency for Research on Cancer (IARC). *Epidemiological classification of HPV types causing squamous cell cervical cancer: Implications for prevention.* New Eng J Med 2003, 348(6): 518-527

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Surgery for primary and recurrent disease

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Standard surgical treatment of cervical carcinoma includes radical hysterectomy for FIGO stages IB and IIA and pelvic exenteration for advanced primary and locally recurrent central pelvic disease without pelvic side wall involvement. Current radical hysterectomy techniques are based on surgical anatomy which is in several aspects not compatible with human embryologic and fetal development. The operation is generally performed without visualization of the pelvic autonomic nerves. Adjuvant radiation is necessary to obtain acceptable local control rates for patients whose carcinomas exhibit histopathological risk factors. The rates of treatment-related severe complications and long-term sequelae appear to be higher than those for primary radiation although the oncological results are not better. The new total mesometrial resection (TMMR) is characterized by (i) the en bloc resection of the uterus, proximal vagina and mesometrium as a developmentally defined entity, (ii) transection of the rectouterine subperitoneal dense connective tissue above the level of the exposed hypogastric nerve and inferior hypogastric plexus and (iii) extended pelvic/periaortic lymph node dissection preserving the superior hypogastric plexus. From 1998 to 2002 71 patients with cervical cancer FIGO stages IB, IIA and selected IIB underwent TMMR without adjuvant radiation. 54% of the patients exhibited histopathological high risk factors. At a median observation period of 30 months 6 patients relapsed and 3 patients died. No patient had grade 3 or 4 complications. No severe long-term impairment of pelvic visceral functions related to autonomic nerve damage was detected. Based on these preliminary results TMMR achieves a promising therapeutic index by providing a high probability of locoregional control at minimal short and long term morbidity. Another new operation, the laterally extended endopelvic resection (LEER) extends the lateral resection plane of pelvic exenteration to the medial aspects of the lumbosacral plexus, sacrospinous ligament, acetabulum and obturator membrane. The inclusion of the muscles of the pelvic side wall and floor as well as the complete urogenital mesentery en bloc with pelvic organs in the LEER specimens allows the removal of a subset of locally advanced and recurrent cervical carcinomas fixed to the pelvic wall with free margins (R0). 36 patients with recurrent (n=29) or primary advanced (n=7) gynecologic malignancies involving the side wall of the lesser pelvis underwent LEER from 1996 until 2002. Severe postoperative complications occurred in 14 patients. Five-year survival probability was 49% for the whole group and 46% for those patients considered only for palliation with current treatment options. Patients without evidence of disease achieved good quality of life.