are associated with presence of a CpG island methylator phenotype (CIMP), codeletions of the chromosomal arms 1p and 19q (1p/19q), and epigenetic silencing of the O^6-methylguanine-DNA methyl-transferase (*MGMT*) gene that are determined routinely in many brain tumor centers due to their diagnostic, prognostic, or predictive value.
MGMT is frequently silenced by promoter methylation and was found to be predictive in glioblastoma for benefit from the addition of the alkylating agent therapy temozolomide to radiotherapy, the current standard of care. A predictive value was recently confirmed in two trials treating elderly glioblastoma patients with either temozolomide or radiotherapy. This had a practice changing impact and requires now MGMT testing for treatment decision. However, in anaplastic glioma *MGMT* methylation has been reported from two clinical trials to be only prognostic. This puzzling result suggested that the molecular context of *MGMT* methylation may be different between these glioma subtypes. Indeed, the genetic and epigenetic context is strikingly different. In glioblastoma loss of one copy of chromosome 10 on which *MGMT* resides (CHR 10q23) is very frequent (>80%) as opposed to anaplastic glioma. Interestingly, in low grade and anaplastic glioma MGMT mutations are highly associated with *CIMP*. Mutations in *IDH* have been found to be an early event, very common in low grade and anaplastic glioma (50-80%), while they are infrequent in glioblastoma (<10%), usually associated with secondary glioblastoma that evolve through evolution of lower grade precursor lesions. Recent publications provided evidence that *IDH1/2* mutations indirectly, through production of an onco-metabolite lead to epigenetic deregulation resulting in CIMP. Hence the epigenetic and genetic context of *MGMT* methylation in glioblastoma is different from anaplastic glioma. Emphasizing that *IDH* mutant/CIMP positive gliomas are patho-genetically distinct entities with different biological and clinical features that respond differently to treatment approaches. These insights need to be taken into consideration for future trial design.Co-deletions of 1p/19q are usually associated with *IDH* mutations, hence oligodendroglial tumors seem to be a favorable subgroup of CIMP associated glioma. Retrospective analysis of two clinical trials for anaplastic glioma suggested that 1p/19q co-deletions are predictive for benefit from the early addition of chemotherapy to radiotherapy a practice changing finding.
Among the many signatures and molecular markers identified in glioma actionable markers are, unfortunately, rare with the currently available treatments. New strategies have to be adopted to test promising drugs in molecularly stratified patient populations.

SP-0535
Reirradiation for recurrent glioma/GBM: Advances in our knowledge of normal tissue tolerance
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Abstract not received

SP-0536
Chemotherapy for recurring glioma/GBM: The optimal treatment techniques
R. Stupp
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Abstract not received

DEBATE: NANOPARTICLE PERSPECTIVE: THIS HOUSE BELIEVES THAT THE MOST EFFICIENT FORM OF PHYSICAL ENERGY IS…

SP-0537
Using x-rays to guide drug delivery
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Current goals of drug design in oncology are to discover and target therapies to specific receptors or antigens on tumors, while simultaneously avoiding systemic toxicity. Even the targeted therapies on the market have notable systemic toxicities, as many of the targets are not unique to tumors. Solid tumors contain a unique micro-environment that is often not conducive to drug distribution. Drugs often reach tumor sites by penetrating across the endothelial linings of the capillaries, but different pressure gradients inside the tumor influence the ability of drugs to extravasate.
One of the unique aspects of using X-ray radiation therapy (XRT) for treating tumors is that it can be delivered to a focused tissue volume. This allows for the deposition of high cumulative radiation doses at the tumor site while sparing the normal surrounding tissues. New research done in the last decade has shown that XRT, although also therapeutic, can induce neoantigens at the cell surface of tumors and tumor blood vessels. The usefulness of neoantigens for therapeutic applications lies in the fact that they are differentially expressed on the surface of irradiated tumor cells to a greater extent than on normal tissues. This differential expression provides a mechanism by which tumor cells can be “marked” by radiation for further targeting. Using phage display biopanning, recombinant peptides that bind preferentially to radiation-treated cancers have been found. Drug delivery vehicles conjugated to ligands that recognize and interact with the neoantigens can help to improve tumor-specific targeting and potentially reduce systemic toxicity with cancer drugs.
For instance, our group has found that glucose regulated protein 78 (GRP78) is present in low levels in normal tissue, shows increased expression in numerous solid tumors, and is upregulated after treatment with XRT, providing a tumor-specific target for drug delivery. The targeting peptide specifically binds to GRP78 post-XRT and not normal tissue which allows for an increased percentage of drug load to be directly delivered to the radiation-treated tumor volume. By using radiation treatment as a means to “mark” the tumor for drug delivery, this new potential form of treatment hopes to dramatically reduce the systemic toxicity that is typically associated with cancer drugs, while simultaneously increasing the biodistribution of these drugs to the tumor region.
In addition to active targeting, alternative methods for tumor-toxic payloads have been created, which capitalize on radiation-induced targets. XRT has been shown to improve the delivery of nanoparticles to tumor cells because it transiently increases the permeability and retention effect of the vasculature after single treatments at clinically-relevant doses. Another strategy is the use of adenoviruses whose transfection rates increase in the presence of ionizing radiation. This same technology has led to the creation of the product TNFerade, in which TNF-alpha is produced by a radiation-inducible promoter but predominantly within the radiation field. This product has been successfully tested in phase III clinical trials.
The characteristics of ionizing radiation that make it an appealing option targeting nanoparticles are multiple. First, it is already ubiquitously used in cancer treatment protocols. Second, when used at low doses for short periods of time, radiation therapy is associated with relatively few side effects. Third, it readily penetrates tissue. Fourth, it can be accurately delivered to specific tumor volumes while sparing surrounding normal tissues. Fifth, it induces site-specific gene transcription and protein expression within cancer. Finally, tumor targeting peptides are being discovered that bind to radiation-inducible receptors; these peptides can be functionalized with nanoparticle carriers to enable radiation-guided delivery of chemotherapy to the tumor microvasculature. Further research exploring these targets for therapeutic purposes as well as in the discovery of novel radiation-induced antigens will aid in improving targeted strategies and the efficacy of radiotherapy.

SP-0538
Using magnetic fields to guide drug delivery to cancer
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Image guided drug delivery requires physical energy that is deposited within cancer to activate drug delivery. The classic example is boron neutron capture. More recently, heat has been used to “melt” liposomes for thermal control of drug delivery. Ionizing radiation is also used to induce the expression of receptors and antigens for targeted drug delivery. Magnetic fields are used to guide drug delivery and oscillate magnetic nanoparticles to heat tumors. Radiation oncologists are uniquely trained in the field of image guided delivery of therapy. ESTRO and ASTRO should develop each of these forms of external administration of energy to control drug delivery. Although these strategies are complementary, they vary in their feasibility to bring drug delivery systems into clinical trials and in their cancer specificity. Each strategy has its limitations. For example, radiation inducible neoantigens and receptors are not induced in every cancer subtype. Magnetic fields are site specific but not cancer specific which could lead to drug delivery throughout the entire magnetic field. Similarly, heat is site specific but not cancer specific and could result in drug delivery to adjacent normal tissues. Moreover, the thermal regulated liposomes can release the drug systemically. Pharmacokinetics of each of these forms of image guided drug delivery vary. For example, thermal regulated drug delivery produces

rapid release of the drug whereas other modalities can have sustained drug delivery. The speakers in this forum will describe the pros and cons of each of the drug delivery systems that are designed to improve bioavailability of cancer chemotherapy to sites of neoplasia.
X-ray guided drug delivery exploits the stress response within cancer that occurs during radiotherapy. Low doses of radiation induce DNA strand breaks and oxidative stress within cancer. Stress proteins such as GRP78, TIP1 and Calreticulin are induced and transported to the surface of cancer cells following irradiation. Antibodies and peptide ligands that are specific to these radiation inducible neoantigens are used to coat the surface of nanoparticles and liposomes for guided drug delivery. This strategy of x-ray guided drug delivery is analogous to military use of lasers to tag targets for smart bombs. X-rays are tissue penetrating and therefore tag deep seated cancers for the binding of antibodies and peptide ligands. The discovery platform for this technology identifies inducible antigens that are specific to cancer and not induced in normal tissues. Antigens that are induced in normal tissues are discarded while cancer specific antigens are developed. These targeting moieties are conjugated to drug delivery systems. In contrast, hyperthermia is used to heat a tumor. As liposomes pass through the tumors, the lipids melt and release the drug in that volume. This strategy of thermal regulation of drug delivery has entered Phase III clinical trials in breast cancer to deliver Doxorubicin. The use of magnetic nanoparticles for drug delivery is still in the preclinical stage. Paramagnetic nanoparticles have been targeted to tumors for both drug delivery and to heat tumors. Oscillating magnetic fields cause these nanoparticles to vibrate and heat the tumor to induce hyperthermia. These three forms of image guided drug delivery will becompared and contrasted during the debate of the practicality of bringing these new strategies of drug delivery into clinical trials.

SP-0539
Using heat to control the release of drugs in cancer
L. Lindner
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Abstract not received

SYMPOSIUM: CLINICAL EXPERIENCE AND CURRENT EVIDENCE (INCL. PLANNING STUDIES) FOR PROTON THERAPY

SP-0540
The level of evidence for proton therapy
M. Pijls-Johannesma
MAASTRO Clinic, Maastricht, The Netherlands

Abstract not received

SP-0541
Evidence- vs. re-imbursement vs. patient-demand based proton therapy
E. Hug
ProCure Headquarters, New York, USA

Abstract not received

SP-0542
Clinical experience and evidence for proton therapy of peaediatric cancer patients
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Proton beam therapy seems to offer significant advantages over conventional techniques especially for the pediatric cohort and the number of children being treated with proton therapy for solid tumors is increasing rapidly throughout the world. There have been multiple dosimetric studies clearly demonstrating that protons decrease the irradiated volume and therefore the dose to the developing normal tissues compared with photon techniques while showing excellent outcome in the pediatric population. As in paediatric malignancies survival rates have increased considerably, from 0-20% until the 50ies up to about 80% today, quality of life (QoL) and late sequelae have become a major concern in pediatric cancer survivors. Therefore, proton therapy was understood as a tool potentially reducing the risk for secondary malignancy induction as well as for late effects. As children are particularly sensitive to radiation injury, they seem to be the cohort taking the greatest potential benefit from sparing dose to normal tissue. Today, local treatment with proton beam in CNS tumors or sarcomas is a common choice to be offered to the pediatric cohort in Europe and in US whenever available.
It is suggested from early reports, that secondary cancer incidence may be reduced by 50% when using proton therapy. Additional early data was published on neurocognitive functioning and quality of life, both suggesting favourable outcome after proton beam therapy. Still, prospective data are limited, cohorts are small and observation times not sufficient, especially when looking at very young children being treated with proton beam therapy.
In conclusion, proton beam therapy is a promising tool to explore particularly in the pediatric cohort to reduce the risk for late effects and secondary malignancies; however, due to limited availability up to now, clinical experience of proton therapy in childhood cancer is still limited. Therefore, all pediatric programs should be accompanied by prospective evaluations of late effects and QoL to gather more information on optimal use of proton therapy. Due to small number of patients and ethical considerations, randomized data will be hardly available even on the long term in children. Still, more clinical data will be emerging to quantify the clinical benefit of proton beam therapy with regard to a decrease in late effects while maintaining excellent cancer control rates.

PROFFERED PAPERS: PHYSICS 11: OUTCOME MODELLING

OC-0543
Patient-specific in vitro measurements of SF2 and Tpot - how well do they predict the tumour control probability?
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Purpose/Objective: The aim of this study is to investigate the predictive value of the modelled tumour control probability (TCP) based on BED calculations using individual measurements of in vitro radiosensitivity (SF_2) and potential doubling time (T_{pot}) for head and neck (H&N) cancer patients versus literature-based average radiobiological parameters.
Materials and Methods: Tumour radiosensitivity, measured *in vitro* on primary biopsies and expressed as surviving fraction of cells following an acute exposure of 2 Gy (SF_2), T_{pot} and tumour size were determined for 46 H&N cancer patients. All patients were treated with external beam radiotherapy and 28 patients also received brachytherapy. For each patient TCP was calculated using a Poisson-LQ model based either on the patient-specific radiobiological parameters or literature-based average radiobiological parameters (α=0.3 Gy^{-1} and T_{pot}=3 days). The predicted TCP values for the two sets of parameters were compared with the actual outcome for the patients in terms of local control.
Results: The average radiobiological parameters lead to a large underestimationof TCP as the predicted TCP was below 10% for the majority of the patients that actually presented local control. When tumour specific parameters were used,the majority of the patients with local control had a predicted TCP larger than 90%. A Receiver Operating Characteristic (ROC) curve analysis was also performed for assessing the predictive values of the two methods for calculating the TCP. The corresponding ROC curves are shown in Figure 1.