Purpose or Objective: Hyperthermia (raising the tumour temperature to 40-43°C) is an effective treatment in combination with radiotherapy for several tumour sites, including cervical cancer, which is mainly caused by infection with the Human Papillomavirus (HPV). The aim of our study is to improve treatment strategies for cervical carcinoma by (#1) unravelling mechanisms of hyperthermia induced radiosensitization, (#2) optimization of time interval between hyperthermia and radiotherapy and (#3) investigating the benefit of additional treatments.

Material and Methods: HPV-positive cervical cell lines SiHa and HeLa were used. Cells were treated with (#1) hyperthermia alone (42°C for 1h), (#2) hyperthermia and irradiation in different time intervals between the two therapies and (#3) hyperthermia and radiation with additional agents PARP1-inhibitor (i.e. a drug blocking a DNA repair protein) and cisplatin. Clonogenic survival assays and γH2AX stainings (a staining to visualize DNA double strand breaks) were carried out in order to determine the effectiveness of the (combined) treatments. Protein levels of p53 and DNA repair proteins were investigated using western blot. Apoptosis was measured in cell lines using the Nicolett assay and cell cycle distribution was analyzed using the BrdU-assay.

Results: (#1) The high-risk HPV types 16 and 18 produce the oncoprotein, early protein 6 (E6), which binds to p53 before both proteins get degraded. Therefore, p53 cannot induce cell cycle block nor apoptosis, limiting the radiation effects. Hyperthermia increases the effectiveness by preventing the formation of the E6-p53 complex, rescuing p53 from degradation, resulting into functional p53 causing apoptosis and cell cycle arrest. (#2) Higher levels of p53 are present immediately after hyperthermia and remain up to four hours after treatment. The main therapy, radiotherapy, chemotherapy, should be applied within this time frame to yield a beneficial effect. (#3) Combination treatment of radiotherapy, hyperthermia, cisplatin and PARP1-inhibitors resulted in a lower survival fraction due to an increased number of DNA double strand breaks as compared to radiation alone. Cisplatin and PARP1-inhibition significantly enhanced the combined hyperthermia/radiation treatment.

Conclusion: Our findings provide new insights for patients suffering from HPV-positive cervical cancer. Hyperthermic-radiosensitization, makes radiotherapy significantly more effective by rescuing p53 from getting degraded. Adding PARP1-inhibitor or cisplatin further improves the effectiveness of hyperthermic-radiosensitization, which will increase clinical outcomes substantially.

**EP-2025**

**The potential role of gold nanoparticles in proton beam radiosurgery for arteriovenous malformations**

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**Purpose or Objective:** To theoretically evaluate therapeutic gain from radiation dose enhancement by gold nanoparticles (AuNP) based on their physical interaction with protons.

**Material and Methods:** Nanoparticles range in size from 1 x 10⁻⁹m to 100 x 10⁻⁹m, and exert their effect by either entering the cell, or by attaching to the cell membrane surface. Radiation enhancement by gold nanoparticles (AuNP) is based on the generation of much localized secondary radiation when irradiated. This results in a Dose Enhancement Factor (DEF) and has been well described for photon irradiation and is most pronounced with kilo voltage photons, but happens also with Mega Voltage (MeV). For protons the DEF obtained with metallic nanoparticles has recently been studied. We took the definition of DEF as being: DEF=(Dpure + DGNP - Dwnp )/ Dpure , where Dpure is the dose deposited in pure water.

**Results:** In vivo studies on tumors in mice have shown a considerable delay in tumor growth for mice receiving AuNPs with protons compared to protons alone. Protons have a high cross-section for gold over a large range of clinical energies, and the interaction produces Auger electrons with a very short range. The sphere of DEF around the AuNP is influenced by its size. For an AuNP of r = 22nm and 80 MeV protons the radius of the sphere of DEF is in the order of 18nm, with dose enhancement factors of up to 2 described. We obtained a value of 1.06 at 1 nm from a nanoparticle with radius 25 nm and taking Dpure as being: Dpure [Gy] = 8.16 x Sw [MeV x cm²/g ] x 5w [MeV x cm²/g], where Sw is the stopping power of water. This small radius means that in order to be effective the AuNPs need to be in very close contact with the target. In the treatment of AVMs the prime target is the endothelial cell. Angiogenesis occurring in AVMs is driven by endothelial cells stimulated by vascular angiogenic factors binding on cell membrane receptors. AVM endothelial cells over express these receptors compared to their counterparts in normal brain vessels. IMC-1121B, a human antibody to VEGFR2ab, when linked with an AuNP has the potential to selectively increase the local AuNP concentration on the membrane of AVM endothelial cells. For conventional dose/fractionation schedules the radiobiological effects are governed by DNA damage in the cell nucleus. Membrane location could also be exploited because a cell membrane initiated effect is described, whereby activation of the acid sphingomyelinase/ceramide pathway occurs after doses >10 Gy, leading to endothelial apoptosis.

**Conclusion:** Successful AVM radiosurgery is amongst others dose dependent. Therapeutic gain in proton radiosurgery is possible with AuNP-VEGFR2ab located on the cell membrane, combined with doses > 10 Gy. This approach needs to be researched further, but offers the possibility for better obliteration rates and/or shorter latent intervals.

**EP-2026**

**Effect of PARP-1 inhibition on human soft tissue sarcoma cells radiosensitivity**

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**Purpose or Objective:** Soft-tissue sarcomas (STS) are aggressive tumours with a poor prognosis and there is a major clinical need for novel strategies. Poly-ADP ribose polymerase (PARP)-1 promotes base excision repair and DNA strand break repair. Inhibitors of PARP (PARPi) have shown to enhance the cytotoxic effect of irradiation (IR), and evidences suggest that PARPi could be used to selectively kill cancers defective in DNA repair. Sarcomagenesis is linked to aberrant biological pathways and some STS have a defect in DNA repair pathways, so there is a rationale for using PARPi in STS. We investigated the effect of PARP inhibition on STS cell lines survival after IR and on radiation-induced DNA damage foci.