Influence of indyvidual low-dose radiosensitivity on the chemopotentiating effect of low-dose fractionated radiation in patients with locally advanced head and neck cancer.

The basis of conventionally fractionated radiotherapy is dose per fraction of 2 Gy given once a day for five days a week continuing for 3-7 weeks. Until recently, doses per fraction <1 Gy were not used in radiotherapy of malignant tumours because they were presumed to be ineffective. The clinical significance of low doses changed when the phenomenon of low-dose hyper-radiosensitivity (HRS) was discovered. The phenomenon of HRS is an effect in which cells die from excessive sensitivity to low doses (< 0.5 Gy) of ionizing radiation, but become more resistant (induced radioresistance, IRR) to larger doses. Compared to conventional radiation doses (2 Gy), low doses are thought to be more effective (per unit dose) because they do not activate cellular repair mechanisms, resulting in all damaged cells being killed. One possibility to benefit in the clinic from HRS effect is by using low-dose fractionated radiation (LDFR) as an enhancer of systemic chemotherapy. The rationale for this treatment strategy came from *in vitro* studies that reported that cancer cells are more sensitive to taxanes and cisplatin combined with low-dose fractionated radiation (4 x 0.5 Gy) than with single dose of 2 Gy. To date, seven phase II clinical trials have been conducted to assess the benefit of combining LDFR with drugs such as taxanes and cisplatin. Although, all these trials confirmed effectiveness and acceptable toxicity of such treatment in patients with locally advanced head and neck, breast, lung, uterine cervix cancer or brain tumours, randomized clinical trials have not been initiated. The reason might be the fact that the exact molecular mechanism underlying the process of chemopotentiation by LDFR remains unclear. It is still not known whether the chemopotentiating effect of LDFR depends on the presence of HRS phenomenon in patients' cells and will benefit all patients.The fact that our National Research Institute of Oncology in Gliwice, as the first in Poland, has started a phase II clinical trial using LDFR (0.5 Gy fractions) as a potentiator for induction chemotherapy in locally advanced squamous cell cancer of the head and neck (SCCHN) gives us a unique opportunity to answer the above questions.
According to a new theory (RIANS, radiation-induced ATM nucleo-shuttling) the response to low- and high-dose radiation depends on the transport of the ATM kinase (a major protein of DSB repair and signaling) from the cytoplasm to the nucleus. Recently, the assay based on the RIANS model in fibroblasts was shown to be one of the most reliable predictors of clinical radiosensitivity. The aim of the present study is to determine (for the first time) the role of the RIANS theory in regard to low-dose radiation and HRS phenomenon. This study will also, for the first time, evaluate the predictive potential of the test based on the RIANS theory in patients treated with induction chemotherapy combined with low-dose fractionated radiotherapy.

In the study, primary normal fibroblast derived from 40 patients enrolled in the phase II clinical study (mentioned above) will be used. Low-dose radiosensitivity and HRS status will be assessed by flow cytometry-based clonogenic survival assay. The radiation-induced ATM nucleo-shuttling in fibroblasts will be investigated by fluorescence pATM and γH2AX foci assays.

As a result of the project, new knowledge about the potential predictive factors and molecular mechanism underlying the process of chemopotentiation by LDFR in patients with head and neck cancer will be added. This knowledge, in turn, should contribute to further exploit low-dose fractionated radiation in the treatment of cancer.