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Interaction of high-LET heavy ion irradiation and etoposide on two cell lines with different radiosensitivities and different p53 status in vitro

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Background: To investigate the differences between two rat yolk sac tumor cell lines with different radiosensitivities in sensitivity to high-LET heavy ion beam and in sensitizing effect of etoposide (DNA topoisomerase II inhibitor) in combination with heavy ion beam.
Material and methods: NMT-1 (wild-type p53 cell) is a parent radiosensitive cell line and NMT-1R (mutant-type p53 cell) is a variant radioresistant cell line. Heavy ion (carbon ion) was accelerated to 290 MeV/u by a heavy-ion medical accerelator in Chiba at National Institute of Radiological Sciences. The dose average LET value in the samples was 80 keV/μm. The effects of carbon ion irradiation were assessed by clonogenic assay. The concentration of etoposide required to reduce colony formation by 50% at 1-hour treatment (IC50 of etoposide) was selected for heavy ion irradiation pretreatment for each cell line. The RBE (relative biological effect) of the carbon ion beams to X-rays was calculated for D_{10}(10% survival dose).
Results: There was no significant difference between NMT-1 cells and NMT-1R cells in sensitivity to high-LET heavy ion irradiation (LET;80keV/im) and no shoulder in dose-response curve. The RBE was 1.41 for NMT-1 and 2.16 for NMT-1R, respectively. The RBE of carbon beam was larger in mutant-type p53 cells than in wild-type p53 cells. Etoposide showed a supra-additive effect in combination with carbon beam irradiation in NMT-1R cells. Etoposide potentiation in NMT-1R cells was manifested by the decrease in the slope of the radiation dose-response curve. However, there was no enhancement effect in radiosensitive NMT-1 cells.
Conclusions: Our findings suggested that high-LET radiotherapy is expected to be effective for patients carrying radioresistant tumors and mutated p53 tumor cells. Etoposide might be effective for radioresistant tumors in combination with heavy ion beam irradiation.

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Quality Assurance (QA) clinical indicators to detect treatment errors and potential overdose in radiotherapy; first results

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Current combined chemo-radiotherapy treatments or combinations with biological modifiers are changing the profile of the expected acute toxicity. Despite the execution of modern automated error-minimization methods and QA procedures, serious human systematic mistakes (0.3–2.5%) remain a source of error in radiotherapy and can occur in each stage of treatment planning and delivery. Dose in excess of 5% leading to increase tissue reactions may not be detected clinically soon enough to prevent significant damage. In order to discrimate potential overdose we have developed two clinical indicators based on the frequency and seriousness of accumulated or single events during radiotherapy treatment. The aim of the study was to analyse the first two year results of these indicators.
Two type of indicators were defined: 1. Patients with >7day gap(7DG) due to toxicity during treatment, and 2. Medical Prescription Rest Rate (MPRR) (defined as the number of prescribed rests for medical reasons divided by the number of delivered treatments) per month and refered to each treatment unit. In order to define the MPRR cut-off value, we retrospectively analysed the chart data of all patients treated in our department during the 2002. We considered this value plus 2 standart deviation (2SD) as the cut-off for every unit. When MPRR exceeded 7% or there was any 7DG, a clinical and dosimetric QA procedure was activated to detect systematic error related to each treatment unit (MPRR) or individual major mistakes (7DG). From January 2003 to December 2004 we have prospectively registered these indicators.
During the studied period 5732 patients were treated in three units: one cobalt, one 6–18 Mv linac (linac1), one 6Mv linac (linac2). The 7DG indicator was activated in 74patients (1.3%). Mean MPRR per unit was 4% (range 1%-11%), 3.3% (range 1%-8%) and 3.8% (range 1%-9%) for cobalt, linac 1 and linac 2 respectively. Table 1 shows the annual figures of the mean MPRR per unit. The MPRR monthly indicator was activated 4 times (11%, 9%, 9%, 8%), twice in cobalt, once in linac1 and linac2 respectively. The case to case QA review procedure showed that 5 patients loosing each one 25 sessions (3 due to expected toxicity and 2 for tumoral progression) were responsible of these MPRR alarms. After the individual review no overdose was stated.

	2003			2004		
	Cobalt	Linac 1	Linac 2	Cobalt	Linac 1	Linac 2
Delivered sessions	10021	8199	8716	12368	9095	11064
Number of Rests	471	268	360	354	330	405
MPRR±2SD	4.7±2.6%	3.2±1.5%	4.3±2.2%	3±1.3%	3.4±1.9%	3.4±1.8%

Despite that the MPRR or >7d gap due to toxicity indicators did not show any overdose, prospective patient related clinical QA procedures are very recommended to detec systematic errors that could escape from established QA process.

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Selenium radiosensitizes prostate cancer cells in vitro: a beneficial adjunct to radiotherapy?

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Introduction: Selenium is an essential trace element in the human diet and epidemiologic data supports its role as chemopreventative agent against prostate cancer. Up to 50% of prostate cancer patients can be ingesting selenium at the time of consultation for radical treatment. However, very little information is available on the potential benefit or harm of this agent during radiotherapy or chemotherapy, given its antioxidant free-radical scavenging properties and its ability to up-regulate DNA excision repair via p53. The present study was designed to determine whether selenium alters the radiosensitivity of malignant prostate cells in relation to normal cells.
Methods: Human prostate cancer cell lines PC-3 and DU-145, mutant and null for p53 respectively, and normal human fibroblasts (NDF strain GM05757) were treated in vitro with 2 μM, 10 μM, 50 μM and 250 μM selenomethionine for 24–96 hrs. The cells were then subjected to 0 to 10 Gy irradiation and clonogenic survival assays were performed. Western blot and flow cytometric analyses were completed to determine cell cycle distribution pre- and post-selenium. Finally, the expression and resolution of gamma-H2AX, a biomarker of DNA breaks, was quantitated to determine the effect of selenium on DNA strand break repair.
Results: Selenomethionine alone was cytotoxic to prostate cancer cells. Selenium radiosensitized DU145 and PC3 cells, but not GM05757 fibroblasts, with dose-enhancement ratios ranging from 1.3 to 1.5. These effects were not correlated to radiation-induced apoptosis. However, radiosensitization of DU145 and PC3 cells was associated with a p53-independent G1 arrest and elevated levels of gamma-H2AX foci.
Conclusions: Selenome thionine leads to increased sensitivity of prostate cancer cells to ionizing radiation, possibly by affecting cell cycle arrest and DNA repair during treatment. It will be important to test selenium as a radiosensitizer in vivo as these results could impact on treatment guidelines for prostate cancer patients during radiotherapy.
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Radiation-induced CD8 T-lymphocyte apoptosis predicts tumor sensitivity in head and neck cancer

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Background: The concept of expecting radiosensitive tumors in patients genetically hypersensitive to radiation is not widely accepted. Here, we aim to assess whether the tumors of patients with increased lymphocyte apoptotic response with head and neck cancer have a better outcome than their normoresponsive counterparts. Materials and
Methods: Seventy-five patients with head and neck cancer treated with curative radiation therapy (RT) were included in the KFS 00539-91997/ SKL 00778–2-1999 prospective study aiming at assessing the value of CD8 T-lymphocyte apoptosis in predicting intrinsic radiosensitivity. Male to female ratio was 60/15, and median age was 59 years (35–85). Median radiation dose was 66 Gy (60–74.4 (administered in median 41 days