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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

(37–58). Dose per fraction was 2 Gy in the majority of the patients (n = 70). Prior to RT, all patients were tested using a rapid (48 h) apoptosis assay where fresh blood samples were irradiated with 8 Gy X-rays. Lymphocytes were collected and prepared for flow cytometric analysis. Apoptosis was assessed by gradual degradation of DNA (sub-G1 peak on the DNA histogram). Acute (CTC v2.0) and late (RTOG/EORTC) toxicities were graded in all patients. Median follow-up period was 31 months (23–43).
Results: Following in vitro 8 Gy irradiation, median radiation-induced CD8 apoptosis was 20.88% (5.69–57.00%). Radiation-induced CD8 apoptosis significantly predicted grade 2 and 3 late effects. The area under the curve of the receiver-operated characteristic curve (sensitivity versus 1-specificity) of CD8 apoptosis was 0.83. Median time to locoregional relapse was 30 months (1–43 months). There were 13 locoregional relapses among the 37 patients showing CD8 apoptosis below the median compared to 5 of 38 who were above (p = 0.02). Two-year estimated locoregional relapse rate was 31% (95% CI: 17–45%) versus 14% (95% CI: 3–25%), respectively (p = 0.03).
Conclusions: In patients with head and neck cancer treated with definitive or postoperative RT, in vivo apoptotic response of CD8 lymphocytes depends on genetic radiosensitivity, and the tumor follows the same genetic radiosensitivity of normal tissues. However, these findings should be confirmed prospectively, and future dose escalation studies could be stratified using the apoptosis assay.

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Tolerance and efficacy of high-dose 3D-Conformal Radiation Therapy (CRT) in cirrhotic patients with small hepatocellular carcinomas (HCC) not suitable for curative therapies

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Background: Patients (pts) presenting with small size hepatocellular carcinoma (HCC) benefit from curative therapies (liver transplantation, surgical resection or percutaneous destruction) when others are only candidates for palliative options. Although conventional external radiotherapy is regarded as little efficient and potentially toxic in cirrhotic pts, 3D-conformal RT (CRT) for single HCC nodules demonstrated promising results.
Methods: Prospective phase 2 trial was conducted in 26 pts with small HCC (1 nodule $\leqslant$5 cm, or 2 nodules $\leqslant$3 cm), Child-Pugh A (15), B (8), 19 males, 7 females, mean age 70 (range 57–88 years), TNM stage I-II, mean tumor size 3.2 cm. The endpoints were the rate of complete tumor response, assessed by contrast-enhanced spiral computed tomography showing disappearance of the arterial contrast enhancement observed on 2 successive examinations at 3 mo interval, and assessment of toxicity, using NCI then RTOG-EORTC scales.66 Gy (2 Gy/fx, 5 D/W) was delivered with CRT, respiratory gating was used for recently enrolled pts. Liver dose-volume histograms (DVH) and normal tissue complication probability (NTCP) values were used to evaluate tolerance of 66 Gy.
Results: Out of the 23 currently evaluable pts, 18 (78%) achieved a complete tumor response, maintained with time (local control), and 5/23 demonstrated no response, after 6 months. 2 pts relapsed on the irradiated tumor bed at 12 and 30 months respectively. No G4 toxicity was observed in 16 Child-Pugh A pts, G3 asymptomatic biochemical toxicity was observed in 2 pts. G4 biochemical toxicity was observed in 2/9 pts, Child-Pugh B (thrombocytopenia, hyperbilirubinemia). Biochemical toxicity G3 was observed in 4 pts. 1 a G3 clinical toxicity (portal hypertensive bleeding), 1 jaundice with edema and ascites at 1 mo.
Conclusion: This phase II trial demonstrate that high Dose 3D-Conformal RT can induce complete tumor response, maintained with time (local control) in 78% of pts, with a good tolerance in cirrhotic pts, especially in Child-Pugh A pts. Nine percent of local relapse have been observed with a 17 months follow-up. This non invasive technique is highly suitable for some central or superior tumor locations, unreachable by percutaneous destruction. The future study will compare percutaneous destruction to 3D-CRT using an accelerated fractionation, in pts presenting with small size HCC. Updated results will be presented at the meeting.

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Comparison of setup accuracy of two commercially available immobilization systems for the treatment of head and neck tumors using simulation CT imaging

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Objective: To compare the setup accuracy, comfort level, and ease of use of two immobilization systems used in head and neck (H&N) radiotherapy.
Methods: 21 patients undergoing radiation therapy for H&N tumors were consecutively assigned to one of two immobilization devices: a standard thermoplastic head-and-shoulder mask fixed to a carbon fiber base (Type S) or a thermoplastic head mask fixed to the Accufix™ cantilever board equipped with the shoulder depression system. All patients underwent planning CT imaging followed by repeated control CT imaging under simulation conditions during the course of therapy. CT images were subsequently fused and Setup accuracy was examined by recording displacement in the 3 Cartesian planes at 6 anatomical landmarks and calculating 3-D vector errors. In addition, the time required for setup and the comfort of the two systems was surveyed.
Results: A total of 64 CT datasets were analyzed. There was no difference in the Cartesian total displacement errors between the two populations at any landmark considered. Total vector displacement in the Type S arm reached a SD of 1.77, 1.78, 2.25, 4.77, 6.87, and 3.38mm at the odontoid, right styloid, left styloid, C7 spinous process, right and left acromial extremities, respectively. The Accufix™ system respective displacements are 1.26, 1.16, 1.08, 7.54, 5.36, and 2.78mm. Nonetheless, there was a trend towards a smaller population mean systemic error for the upper landmarks as a single group favoring the Accufix™ system. There was no difference in the setup time required and comfort level between the two systems.

Mean Systematic 3D errors in 21 patients treated for head and neck tumors [a]

Immobilization Device	Systematic 3D error (mean ± 1SD, mm)							
	Odontoid	Styloid		C7 Spinous process	Clavicle		Landmarks	
		Right	Left		Right	Left	Upper[b]	Lower[c]
Type S	2.88 ±1.21	2.91 ±1.44	3.57 ±2.06	8.83±3.13	10.04 ±6.07	5.08 ±2.08	3.12 ±1.59	7.98 ±4.52
Accufix™ System	3.00 ±0.96	2.60 ±0.91	2.71 ±0.91	10.21±7.24	8.03 ±5.13	5.65 ±2.37	2.77 ±0.92	7.96 ±5.47

[a] Setup errors were assessed for each anatomical landmark according to the type of device (10 patients for Type S and 11 patients for the Accufix™ System).
[b] Odontoid, right and left styloid.
[c] C7 spinous process, right and left clavicles (acromial extremities).

Conclusions: No significant difference in 3D setup accuracy was identified between the standard thermoplastic head-and-should mask system and the thermoplastic head mask fixed to the Accufix™ system. The study reassures us that our technique provides accurate patient immobilization, allowing us to limit our PTV to <4 mm when treating H&N and base of skull tumors.

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The impact of half-body irradiation on quality of life of patients with multiple bone metastases

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Background: Half-body irradiation (HBI) is palliative treatment of cancer patients with painful, skeletal dissemination. Using HBI, we obtain pain relief and decrease of analgesics intake. The aim of this study was an evaluation of HBI impact on quality of life (QL).
Material and methods: Material comprised of 80 patients (38 W, 42 M), aged from 31 to 83 (mean 61) treated by one fraction HBI because of multiple skeletal metastases. The most frequent diagnoses were breast (26) and prostate (24) cancers. The most numerous histopathological diagnosis was adenocarcinoma (53). 29 patients had upper (UHBI), 47 lower (LHBI) and 4 middle (MHBI) HBI. The dose of 6 Gy was delivered for UHBI and 8 Gy for L and MHBI. All patients were examined in HBI day, 2 weeks later, and next every month. The pain intensity in 11 degree scale (0–10), performance status (PS) and QL in 7 degree scale (1 - very bad, 7-excellent), and pain frequency in 4 degree scale (1 - never, 4- very often) were evaluated using EORTC QLQ-C30 form. Means of particular variables