516 POSTER

Combined effects of SU5416 and fractionated radiotherapy in tumor xenograft model

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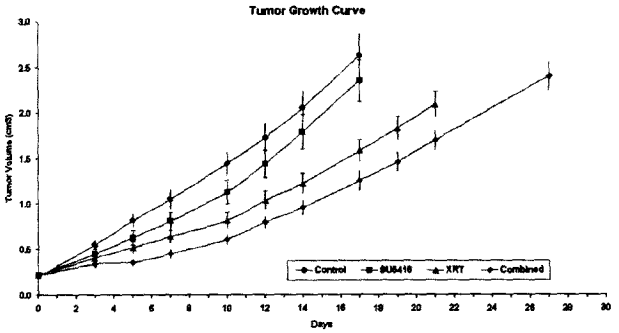
Background: Angiogenesis is critical for tumor development, growth and metastasis. Vascular endothelial growth factor (VEGF) is one of major regulators of angiogenesis. This study aimed to evaluate the combined effects of fractionated radiotherapy and SU5416 specifically inhibiting VEGF receptor 2 in tumor xenograft model.

Material and methods: NCI-H460 human lung cancer cells were inoculated into the thighs of 5-6 week old female athymic nude mice. Tumor volume was measured three times a week in 3 directions (width a, length b and thickness c) and calculated as 0.5abc. After tumors grew to a volume of 0.2 cm^3, treatment started with fractionated radiotherapy and/or SU5416. Radiation was delivered to tumor areas using a ^{60}Co irradiator with daily fraction of 2 Gy for 5 consecutive days (D0-4) and SU5416 of 25 mg/kg was administered i.p. every other day (D0/2/4). Treatment groups (20 mice each) consisted of control, SU5416 alone, radiation alone and SU5416 plus radiation. Tumor growth delay for a given treatment was calculated as the mean time it took for tumors to grow from 0.2 cm^3 to 2.0 cm^3 minus the mean time for control tumors. Dose enhancement ratio(DER) was also calculated using the equation; Tumor growth delay of combined treatment group minus that of SU5416 alone group divided by that of radiation alone group.



Results: There was no difference in weight change between 4 groups during the measurement period. Tumor growth delay for the treatment groups was 1.2 days in SU5416 alone group, 6.6 days in radiation alone group and 10 days in combined treatment group. DER was 1.33.

Conclusions: Combined use of SU5416 and fractionated radiotherapy showed moderate radiation enhancement effects in xenograft model using our drug dosage and administration schedule.

517 POSTER

Dose-dependent upregulation of YKL-40 by irradiation in human glioblastoma cells

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YKL-40 is a 40 kD extracellular matrix protein and a member of the mammalien chitinase-like proteins. YKL-40 stimulates proliferation of fibroblasts, endothelial cell migration and tube formation. YKL-40 has been proposed to be involved in tissue remodeling processes including cancer invasion and metastasis. Recently, YKL-40 has been found to be the most differential expressed gene in a microarray analysis of 19 glioblastoma multiforme (GMB) samples compared to normal brain tissue. A similar result was found in an oligoarray analysis of 4 GMBs versus normal brain tissue. Likewise, results in the SAGE database indicate high YKL-40 expression in GMBs compared to normal brain tissue. Serum levels of YKL-40 are elevated in high grade gliomas and have been suggested as a serum marker for malignant human gliomas, as well as a prognostic marker in several other cancers.

We have investigated 3 human glioblastoma lines for YKL40 expression. All three lines had YKL-40 mRNA expression but only U87 secreted YKL-40 protein in measurable amounts. U87 was investigated for YKL-40 expression after ionizing radiation. Cells were exposed to 0, 2, 5, 10, and 20 Gy of ionizing radiation and conditioned media was harvested after 24 and 48 hrs. The YKL-40 level in the media was determined by ELISA. A dose-dependent increase in YKL-40 production up to more than 3-fold was found 48 hrs after radiation. This was confirmed on the mRNA level by Northern blot. mRNA was harvested 18, 24 and 48 hrs after radiation and interestingly, the rise in YKL-40 mRNA was not observed until 48 hrs after radiation. Again we found a dose dependent response.

The late but pronounced rise in YKL-40 levels after irradiation indicates that YKL-40 production is a downstream response mediated by other proteins rather than an immediate response to radiation. The increase in YKL-40 levels after irradiation suggests the involvement of YKL40 in a cellular stress response, which is in agreement with earlier reports of YKL-40 expression during inflammation and tissue remodeling - two processes involved in the progression of malignancy.

518 POSTER

Carbon ion beam treatment at the Hyogo Ion Beam Medical Center (HIBMC)

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Background To confirm the acute toxicity and response for patents with so called radio-resistant tumor treated by carbon ion beams in the HIBMC as well as stability of the treatment machine.

Material and methods Thirty patients with malignant tumor originated in head & neck (19 patients), lung (3), liver (6), or bone & soft tissue (2) were enrolled in a clinical trial based on the Good Clinical Practices regulated by the Minister for Health, Labour and Welfare in Japan. Patients were required to have an ECOG performance status of grade 2 or less, localized tumor within 12 cm in diameter and WBC >= 3,000/mm3. The relative biological effectiveness of carbon beams was 1.23 to 2.56 by preclinical investigations. There were 17 males and 13 females. All patients had radio-resistant tumor consisting of malignant melanoma in 8, hepatocellular carcinoma 6, adenocarcinoma 5, adenoid cystic carcinoma 4, esthesioneuroblastoma 2, undefferentiated carcinoma 1, mucoepidermoid carcinoma 1, clear cell carcinoma 1, liposarcoma 1 and chordoma 1. Treatment planning was performed using a 3-D radiation treatment planning system. When treating patients with lung or liver cancer, respiratory gating system was used. Just after irradiation, treatment volume was confirmed by auto-activation positron emission tomography. Prescribed dose was 57.6 gray equivalent (GyE) to the 4MVX rays /16Fr/4wks in H & N cancer, 68.4GyE/9Fr/3wks in lung cancer, 52.8GyE/8Fr/2wks in liver cancer, and 70.4GyE/32Fr/8wks in soft tissue and bone tumor. The acute toxicity was assessed according to the criteria of the NCI-CTC up to 90 days after starting carbon irradiation. Objective tumor response was evaluated at the four to six weeks after completion of the treatment using both the WHO criteria and FDG-PET images.

Results Full courses of carbon therapy consisted of 443 portals in the 30 patients were given exactly as scheduled without any trouble of the accelerator or treatment system. Average beam time per fraction was 97 sec. No patients experienced severe acute local reactions more than grade 3. Two patients were CR, 16 PR, and 12 NC. The response rate (CR+PR) was calculated 60%. Of 26 patients who were evaluable in FDG-PET, 21 (80.8%) decreased in standardized uptake value of the tumor after treatment.

Conclusions Our treatment units and systems are safe and reliable enough for carbon irradiation to be used for several malignant radio-resistant tumors localized in the body.

519 POSTER

Technical factors associated with radiation pneumonitis after adjuvant breast irradiation

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Background: To assess the incidence of, and clinical factors associated with clinically significant symptomatic radiation pneumonitis(RP), which requires steroid medication after tangential breast/chest wall irradiation with or without regional lymph node radiotherapy.

Material and methods: The records of 208 patients irradiated with tangential photon fields for breast cancer with more than 2 follow-up visits over 6 months were reviewed. Data on clinical factors previously reported to be associated with RP were collected. Actual and percent irradiated lung volumes receiving more than 20Gy were measured from CT-based treatment plan.

Results: Average (± standard deviation) actual and percent irradiated lung volume for breast/chest wall irradiation were 169 (± 14.9) cc and 14.9 (± 3.8) %, respectively. Addition of regional lymph node irradiation resulted in increase of 183 (±80.2) cc in actual irradiated lung volume and 16.5 (±6.2) % in percent irradiated lung volume. RP developed in 11/208 (5.3%) patients. There was an increased incidence of RP among patients treated with loco-regional radiotherapy (10.3%) vs. those receiving local radiotherapy only (2.5%) (p = 0.02). Previously reported clinical factors associated with RP, such as smoking, underlying lung disease, chemotherapy exposure, use of tamoxifen, failed to show statistical significance in this study. Radiotherapy related parameters, such as actual irradiated lung volume and percent irradiated lung volume were also not statistically related to development of RP.

Conclusions: RP was a rare complication, both with local and loco-regional RT. The addition of regional lymph node irradiation increased the incidence of RP. Failure to show correlation between actual or percent irradiated lung volume and RP may be due to majority of the patients receiving radiotherapy to less then significant actual or percent lung volume.

520 POSTER

Estimation of dose constraints using biologically-normalized dose-volume histogram (BN-DVH) for hypofractionated radiotherapy in the treatment of prostate cancer

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Background: Improvements in prostate cancer treatment techniques have allowed dose-escalation to be achieved by non-conventional fraction sizes (e.g. > 2.4 Gy/fraction), reducing the overall number of fractions from 35-44 to 20-28. The aim of this study is to determine the equivalent range of dose-constraints for rectum and bladder between conventional fractionation and hypofractionation treatment plans.

Materials and Methods: Dose volume histograms (DVHs) for bladder and rectum from ten treatment plans for T1-T2 prostate cancer patients treated with 73.5 Gy (isocentre)/35 fractions/7 wks are exported from ADAC Pinnacle planning system into a spreadsheet with 500 bins per DVH. Each dose-bin is converted to its biological equivalent dose based on the linear quadratic model using alpha/beta ratio of 3. Cumulative biologically-normalized DVHs (BN-DVH) based on this conversion are generated and collated. The average BED D50, D35, D25, and D15 from the BN-DVH and their equivalent doses as given over 16 fractions are calculated using the linear-quadratic formula.

Results: Preliminary results from the first five rectal and bladder DVHs show wide ranges of D50, D35,&etc, for treatment given over 35 fractions (Table 1). The range of values seen at each volume-dose bin is amplified after conversion to BN-DVH.

Table 1: Preliminary results of DVH constraints for conventional fractionation vs. hypofractionation using BN-DVH calculations

	Average Dose over 35# (range)	Average Dose per BN-DVH (range)	Average Dose over 16# (range)
Rectum D50	46 Gy (38-56)	67 Gy (52-85)	37 Gy (31-45)
D35	55 Gy (41-66)	85 Gy (58-107)	44 Gy (34-52)
D25	62 Gy (51-70)	100 Gy (77-117)	49 Gy (41-55)
D15	70 Gy (68-72)	117 Gy (112-122)	55 Gy (53-56)
Bladder D50	38 Gy (25-51)	52 Gy (31-76)	31 Gy (21-41)
D35	49 Gy (39-60)	73 Gy (54-95)	40 Gy (32-48)
D25	56 Gy (41-68)	87 Gy (58-112)	45 Gy (34-53)
D15	66 Gy (59-71)	108 Gy (93-119)	52 Gy (47-55)

Discussion: The BN-DVHs seen in this sample of patients suggest a prescribed dose of 55 Gy/16 fractions would achieve dose-constraints similar to conventional treatment over 35 fractions. The influence of the number of fractions (e.g. 16 vs. 20 vs. 28), the value assigned to the alpha/beta ratio (e.g. 2.5, 3.0, 3.5, 4.0), and the potential advantage in normal organ sparing using IMRT over 3D conformal planning will be examined and presented.

521 POSTER

The use of electronic portal image device (EPID) in the isocenter verification in stereotactic radiosurgery

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Background: The Winston-Lutz test (W-L test) is used as a standard method of isocenter verification in Stereotactic Radiosurgery (SRS). The W-L test is based on x-ray portal image that disable direct digital analyze. The aim of the paper is to present the new method of isocenter verification based on EPID.

Methods and Materials: Linear accelerator Clinac 2300C/D (Varian) equipped with EPID and BrainLab stereotactic accessory including micro-Multileaf Collimator (mMLC) and EPID were used. Digital verification method is based on W-L test, however in digital verification method it is EPID that collects images in order to precise verification of isocenter. During digital verification method mMLC leaves are set to H' shaped field (two pairs of leaves in the middle of the field form small square gap). Then first two portal images are taken. Using laser positioners a small metal phantom ball is located in isocenter. To check isocenter invariability several portal images are obtained at various collimator, gantry and couch positions. After each portal field acquisition a quick visual and digital check is done to control if ball is inside square formed by mMLC. The idea of digital analysis is to subtract two portal images: one with phantom ball and second without ball in the same collimator position. Digital check is performed by independent computer program WinIzo'; developed in Treatment Planning Unit in Center of Oncology Institute in Gliwice, Poland. Digital analyze subtract two portal images (first without ball, second with ball, both with the same collimator position) and shows optical density symmetry distribution.

Results: Isocenter verification method based on EPID and WinIzo application enables to obtain and compare results presented in visual and digital form. Moreover, images analyze is improved. The correction of ball position can be done after each single portal acquisition and there is no need to wait till the whole test is preformed (as in basic W-L method).

Conclusions: Comparing to standard W-L test, presented method is faster, less expensive and more precise. The EPID based method is a standard Quality Assurance procedure in Center of Oncology Institute in Gliwice, Poland.

522 POSTER

Safe integration of high dose rate endoluminal brachytherapy in the conservative treatment of patients with esophagus cancer and external beam radiation with or without chemotherapy

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Background: The current study addresses the feasibility and outcome of treatment with high dose rate endoluminal brachytherapy as a boost and external beam radiation with or without chemotherapy for patients with oesophagus cancer from a single institution experience.

Material and Methods: Patients with either squamous or adenocarcinoma and no metastatic disease were eligible. Brachytherapy was given once or twice weekly to a dose of 20 Gy in 5 fractions prescribed at 1 cm in combination with external beam therapy. The dose prescription was either 50 Gy in 25 fractions with 2 cycles of concurrent chemotherapy using 5-Fluorouracil at 1000mg per Meter Square per day, 96-h continuous perfusion and Cis-platinum at 75 mg per Meter Square on day one, on weeks 1 and 5; or 35Gy in14 fractions alone for patients with karnosky performance of $\leq$ 70. Toxicity was scored using the RTOG acute toxicity scoring system. The primary outcomes were: treatment related toxicity, local control and the functional results prior to local recurrence. Statistical analyses were done using Kadplan-Meir methods.

Results: 45 patients were treated with radical intent. There was an equal distribution between adenocarcinoma and squamous cancer. The mean age was 70 years (range: 45-89). Thirteen patients received brachytherapy and external beam radiation and 32 patients were treated with brachytherapy, chemotherapy and external beam radiation. No patient developed a perforation or fistula during our study. There was no treatment related death. The incidence of Grade 2 toxicity for esophagus was 85%, for bone marrow 55% and Grade 3 hematological toxicity was seen in 15% of patients. The mean follow up was 20 months (range 6-70 months). The actual 2 year and 5 year local recurrence rates documented by biopsy were 33%