surrounding normal tissues. We retrospectively evaluated the safety and efficacy of high dose proton beam therapy (PBT) in patients with stage I non-small cell lung cancer (NSCLC).
Material and Methods: Between December 1999 and September 2006, 77 patients with stage I NSCLC were treated by PBT in our institution. The indication of PBT were (1) clinical stage I NSCLC, (2) PaO2 > 60 torr, (3) medically inoperable, or refusal of surgery, (4) performance status 0−2, (5) written informed consent. The target volume was defined as the gross tumor volume plus appropriate margins for subclinical tumor extension, set-up error and respiratory motion. Treatment was performed using respiratory gating. A total dose of 70−94 Gy_E was delivered in 20 fractions over 4 to 5 weeks. Kaplan-Meier method and CTC-AE version 3.0 were used to assess survival and toxicity.
Results: Patients characteristics were as follows: median age 75 years (range, 52 to 87); male/female, 54/23; Stage IA/IB, 43/34; squamous/adenocarcinoma/others, 28/23/26; total dose 70/80/88/94 Gy_E, 3/57/16/1. The initial response rate was 74% (95% confidence interval (CI), 63 to 83%). With a median follow-up period of 24 months (range, 3 to 82 months), the 2-year local progression-free and overall survivals were 94% (95%CI, 87 to 99%) and 91% (95% CI, 83 to 99%), respectively. No severe acute toxicity was observed. Late grade 2 and grade 3 pulmonary toxicities were observed in 5 and 3 patients, respectively. Four patients experienced fractures of ribs within irradiated volume. The 2-year loco-regional progression-free survivals in stage IA and IB patients were 95% (95% CI, 88 to 100%) and 67% (95% CI, 50 to 84%), respectively. Six of 8 patients who suffered late grade 2 or greater pulmonary toxicities had stage IB disease.
Conclusions: Updated results shows that PBT is a promising treatment modality for stage I NSCLC, although loco-regional recurrences and late pulmonary toxicities in stage IB patients were substantial. Further investigation of PBT for stage I NSCLC is warranted.

910 POSTER

MVCT image-guidance for abdominal and retroperitoneal IMRT target volumes

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Purpose: Mega-voltage CT (MVCT) image-guidance afforded by the TomoTherapy HiArt helical tomotherapy system provides limited soft-tissue contrast and has not been evaluated with regard to its utility in localizing upper abdominal and retroperitoneal soft-tissue radiation target volumes. We analyzed automated system generated patient translational and rotational corrections to match simulation target setup based on mutual information fusion (MI), and evaluated if the MVCT image quality was sufficient to judge the accuracy of MI image-fusion. We assessed how often subsequent user interaction was needed for optimized target setup and compared MI fusion derived positional corrections with user setup corrections.
Results: In 159 MVCT studies of 14 patients with typical upper abdominal and retroperitoneal radiation target volumes, user setup corrections were required for optimized target setup in 84.3%. Mean absolute x, y, z corrections suggested by MI fusion were 3.1, 4.4, and 7.8 mm; mean rotation was 0.5 degrees. Mean respective user setup corrections were 3.7, 5.9, and 9.2 mm, with rotations of 1.0 degree. The mean 3D vector of setup correction was 10.6, and 13.1 mm by MI, and user assessment, respectively. Differences in 3D vector length between automated and user setup exceeded 5, 10, and 15 mm in 25%, 11.2%, and 3.9%, respectively. Automated MI fusion provided on average 76% of the setup correction established by the expert user. MVCT image quality did not allow assessment of MI fusion quality in 7/159 attempts (4.4%). MVCT image quality was judged good, fair and poor in 71 (46.7%), 66 (43.4%), and 15 (9.9%) of the remaining attempts. Operative clips aided in establishing appropriate setup, while gas in stomach and bowel caused detriments in image quality. Targets embedded into soft tissue organs such as liver metastases and hepatobiliary tumors were generally poorly visualized.
Conclusion: Despite the limited soft-tissue contrast, MVCT can be a valid imaging modality for image-guidance of upper abdominal and retroperitoneal soft-tissue radiation target volumes. However, in individual patients and in the absence of fiducials within the target volume, MVCT may fail to provide imaging allowing discerning a soft-tissue target volume. While the system integrated automated image-fusion provides for a seamless clinical workflow, expert user online target location assessment was frequently needed to derive an optimal target setup for tomotherapy delivery.

911 POSTER

Changes in the process of care for small-cell lung cancer (SCLC): Results of the 99-01 Patterns of Care Study (PCS) nationwide survey in Japan

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Background: This study was undertaken to evaluate evidence-based changes in the care process for small-cell lung cancer (SCLC) in Japan through the Patterns of Care Study (PCS) nationwide survey.
Materials and Methods: From July 2002, the PCS conducted a second nationwide survey of care process for stage I-III SCLC patients treated with thoracic radiotherapy (TRT) between 1999–2001. PCS investigated; (1) patient background, (2) work-up studies, (3) process of TRT, and (4) process of chemotherapy. Practice patterns of 99−01 PCS were compared with those of 95−97 PCS.
Results: By using two-stage cluster sampling, the PCS collected data for 139 eligible SCLC patients (men to women ratio, 5:1; median age, 69; age >70, 43%; KPS > 70, 73%; stage III, 89%). Pre-treatment work-up study included chest CT in 96%, fiberoptic scope in 93%, brain CT or MRI in 86%, bone scintigraphy in 79%. The median total dose of TRT was 5000 cGy. Twice-daily radiotherapy (BID) was used in 43%. The median field size of TRT was 12 × 14 cm, including ipsilateral hilus in 96%, ipsilateral mediastinum in 96%, contralateral mediastinum in 84%, and contralateral hilus in 17%. Field reduction during TRT course in 61%. The most predominantly used photon energy was 10 MV (77%), whereas obsolete technique using Co-60 or X-ray energy <6 MV comprised 12%. 3D-conformal therapy was used in 12%. Dose prescription was at an isodose line in 15%. CT-simulation was performed in 40%. Only 12 patients (9%) received prophylactic cranial irradiation (PCI). Ninety-two percent received systemic chemotherapy, of those, platinum based chemotherapy constituted 98%, and 73% were treated by concurrent chemoradiation (CCRT). Treatment by IRB-approved protocol was only 6 cases (4%). Compared with the previous 95−97 PCS, significant increases in the use of CCRT (37% to 73%, P < 0.0001 by Chi-square test), BID-TRT (19% to 43%, P < 0.0001), and PCI (2% to 9%, P = 0.01) in the management of SCLC could be detected, although the absolute number of patients receiving PCI was still extremely low.
Conclusions: Evidence-based CCRT and BID-TRT had well penetrated into clinical practice, however, PCI has not yet widely accepted in Japan.

912 POSTER

Linac based helical intensity modulated total body irradiation

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Background: Total body irradiation (TBI) is frequently used in a conditioning regimen for patients undergoing bone marrow transplantation. While achieving a high level of success, TBI does carry with it significant risk for early and late toxicity, particularly for lung. The ability to selectively lower radiation dose to the lungs may reduce the incidence of symptomatic and life-threatening pneumonitis and allow TBI to be used in cases where compromised lung function would have previously precluded this. We present a new linac based treatment modality for TBI, which allows us to limit dose to organs at risk such as lungs and kidneys, without compromising dose to the rest of the body.
Materials and Methods: Our technique makes use of a helical beam delivery path defined by simultaneous gantry rotation and couch translation. MLC leaf positions and dose-rate are derived using a novel aperture based optimization method. Potential advantages of this technique are (1) critical structures may be spared without compromising target coverage, (2) a conventional isocentric 6MV linac and standard treatment couch is used, (3) on-board kV imaging may be used to monitor patient position on a daily basis, (4) helical beam delivery eliminates the need to turn the patient from prone to supine as is currently required in some standard TBI delivery methods.
Results: We will present treatment planning results obtained for our Varian Clinac iX linac. The first objective is to reproduce the dose distribution achievable in our current TBI technique (uniform dose ±10% to the entire body using a Cobalt-60 sweeping beam). Next we develop optimization strategies that allow conformal avoidance of critical normal structures (rather than defining a limited target such as total marrow or lymphatic system, which may risk higher relapse rates).

We present the dosimetric validation of this technique by comparing Monte Carlo calculated dose distributions to phantom measurements. A Monte Carlo dose calculation algorithm is used since the dose delivered to bones and lungs is of central interest for TBI. For this purpose, we employ a newly developed method for performing fast Monte Carlo simulations for moving radiation sources.
Conclusions: This method could potentially replace our conventional TBI technique allowing conformal sparing of organs at risk leading to improved quality of life and higher survival rates.

913 POSTER

Recombinant Human Keratinocyte Growth Factor (rHuKGF, Palifermin) inhibits CD105 expression in mouse tongue during fractionated irradiation

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A significant reduction of radiation-induced oral mucositis by Palifermin has been demonstrated in various studies. We have shown earlier in a mouse tongue model that the protective effect of Palifermin is not only restricted to the mucosal tissue, since Palifermin also inhibited acute inflammatory changes in the blood vessels of submucosa and tongue muscle. Whether immune responses, including changes in macrophage biology are involved in the development of radiation-induced oral mucositis and underlying inflammatory reaction is not clear. Therefore, the aim of the present study was to evaluate: (1) the effect of radiation alone on the number of activated, i.e. CD105-positive macrophages in mouse tongue, and (2) the possible effect of Palifermin on these processes.
Daily fractionated irradiation, 10×3 Gy/2 weeks, was given to the snouts of the animals. One group of animals received irradiation alone. Single subcutaneous injections of Palifermin (15 mg/kg) were given to another group on day −1, relative to the first radiation fraction at day 0. Three untreated animals served as controls. Groups of 3 mice were sacrificed from day 1 to 16 and the tongues were processed for CD105 immunohistochemistry. The number of CD105-positive macrophages in the tongue tissue was counted. Additionally, the intensity of CD105 staining within the blood vessels, i.e. in fixed blood serum, was determined using an arbitrary score (0−3).
Fractionated irradiation increased the number of CD105-positive macrophages throughout the study period. Values increased from 4.5 ± 1.0 per microscopic field in controls (mean$\pm$SEM) to a maximum of 20.1 ± 4.2 at day 2 after the onset of the treatment. In clear contrast, with administration of Palifermin at day −1, no significant changes in the number of these cells were seen. Additionally, fractionated irradiation increased the intravascular level of CD105 from 0.6 ± 0.3 (arbitrary units, mean$\pm$SEM) in controls to a maximum of 2.6 ± 0.1 at day 14 after the start of the treatment. Similarly, in irradiated and Palifermin-treated animals, no significant increase in serum CD105 expression was found.
In conclusion, a single administration of Palifermin before the onset of fractionated irradiation resulted in an inhibition of the macrophage response in mouse tongue. However, additional studies are required to evaluate further the significance of these findings and their interaction with other, e.g. epithelial pathogenetic mechanism leading to oral mucositis.

914 POSTER

A novel strategy to overcome rdioresistance: selective inhibition of mitochondrial DNA polymerase gamma by vitamin K compounds

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Background: Although several molecular candidates against radioresistant mechanisms were previously proposed, few strategies have been successfully applied in clinics. Here, we demonstrate a novel strategy that selective inhibition of DNA polymerase gamma, which plays a critical role for mitochondrial DNA replication and repair, induces a strong cytotoxicity in various human cancer cells. The purposes of this study are to investigate cellular events induced by the DNA polymerase gamma inhibition by vitamin K compounds, and to explore a novel strategy against radioresistant or recurrent cancers.
Materials/Methods: Human cancer cell lines (Colorectal: HCT116 wild-type, HCT116 p53−/−, HCT15, SW620; Prostate: LNCap, PC3, DU145; Liver: HepG2, Pancreas: Panc-1, Uterus: HeLa, Breast: MCF-7, and Hematological: HL60, Raji) were used for the evaluation of cytotoxicity by vitamin K compounds (VK1, VK2, and VK3). Radioresistant clones were originally established from HCT116 cells MTT assay and colony forming assay were used for the evaluation of cytotoxicity. For the evaluation of occurrence of apoptosis, annexin-PI assay using flow cytometer was performed. Cellular superoxide and hydrogen peroxide were measured by flow cytometer analyses using dihydroethidine (HE) and 5-carboxy-dichlorodihydrofluorescein diacetate (c-DCF) staining, respectively. Mutation or heteroplasmic changes in mitochondrial DNA (mtDNA) were analysed by a direct sequencing.
Results: Cytotoxicities of VK1, VK2, and VK3 in terms of IC50 to those cancer cells were >100 μM (median, >100 μM), 25–100 μM (median, 100 μM), 5−10 μM (median, 8 μM), respectively. Interestingly, VK3 also showed a strong cytotoxicity to the radioresistant clones (IC50: 8.7 μM), while anti-cancer drugs such as doxorubicin, cisplatin, camptotecin, and taxol showed minimum effect on the radioresistant clones. Moreover, VK3 and radiotherapy showed a synergistic effect on both parental HCT116 cells and those radioresistant clones. VK3, but not VK1 or VK2, inhibited the DNA polymerase gamma activity leading to great amount of superoxide generation in both dose-dependent and time-dependent manners, while it induced minimum hydrogen peroxide generation. All vitamin K compounds did not inhibit other DNA polymerase activities. The superoxide generation caused heteroplasmies of mitochondrial DNA, and also induced apoptotic cell death, leading to cytotoxic and growth inhibitory effects by VK3.
Conclusions: VK3 could be a novel and effective strategy against various malignancies and radioresistant cells. Inhibition of the mitochondrial DNA polymerase gamma by VK3 leading to superoxide generation seemed to be a major mechanism of the cytotoxicity. Showing the synergy with radiotherapy, the DNA polymerase gamma inhibition by VK3 may pave the way to overcome radioresistance.

915 POSTER

Enhancement of glioma cell line radiosensitivity by the DNA methylating agent Temozolomide

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Background: Temozolomide (TMZ), a DNA methylating agent, is currently undergoing clinical evaluation for cancer therapy. Because TMZ has been shown to increase survival rate of patients with malignant gliomas when given combined with irradiation (IR), we investigated a possible molecular mechanism behind TMZ's radiosensitizing effect in U251 human glioma cells.
Materials and Methods: Human glioma cells (U251) exposed to [50 μM] TMZ for 1 hr followed by a change media with drug-free one were given IR with single dose of 2 Gy. At various times after IR, we investigated the Clonogenic assay, assesment of double strand DNA breakages (DSBs) and repairement, cell cycle analysis, and various types of cell death pathway after DSBs. In vivo animal study was done with 4 to 6-week-old female SCID mice.
Results: Clonogenic assay confirmed an increase in radiosensitive with dose enhancement factors of 1.32. Evaluation of γH2AX foci showed increased expression in each treated cells. Treatment with TMZ + IR did modify the time course of γH2AX foci expression in irradiated cells. At 24 hr, the number of γH2AX foci per cell expressing was significantly greater in the TMZ + IR treated cells (21.9 ± 2.14 vs. 8.43 ± 1.4 with IR alone and 7.97 ± 1.22 with TMZ alone, $P < 0.05$). However, this TMZ + IR treatment protocol did not result in a redistribution of the cells into a more radiosensitive phase of the cell cycle or in an increase in apoptosis and senescence. Mitotic catastrophe, on the other hand, was increased in TMZ + IR combination than in either single modality treatment (21.6% vs. 9% with TMZ alone and 10.3% with IR alone, $P < 0.05$). In tumor growth delay studies, the TMZ + IR combination resulted in a synergistic inhibition of tumor growth as compared with the individual modalities.
Conclusions: These results indicated that TMZ can enhance radiosensitivity and suggest that this effect may involve an increased occurrence of mitotic catastrophe following DNA damage.