713 PUBLICATION

Non invasive tissue diagnostic by means of backscattered light

R. Jindra[1], H. Kolbabek[2], A. Kubin[1], W. Dobrowsky[2]. [1]City Hospital of Vienna-Lainz, Ludwig Boltzmann Institute for Clinical Oncology and Photodynamic Therapy, Vienna; [2]City Hospital of Vienna-Lainz, Radiooncology, Vienna, Austria

Purpose: To use a small power laser for tissue diagnosis especially in oncologic patients presenting with apparent or occult malignant disease on an out-patient basis avoiding invasive methods.

Methods: We developed a device based on backscattered light from tissue. It consists of a small pen like power laser (power output 0.8 Milli-Watt) at a wavelenght of 670 Nanometer. The laser output is placed on the tissue surface. In contrast to most methods which use tissue dependent absorption we look at the backscattered light whereby scattering exceeds absorption in case of (normal) biological tissue about two orders of magnitude. Backscattered light is guided by a glass fibre to an optio-electrical converter. This is realized by a transimpedance sensitive transimpedance amplifier with an upper bandwith of 1 KiloHertz. Only the time dependent share of the signal (in the range of some 10 to 100 PicoWatt) is further amplified, filtered to reduce the overall bandwith from 1.5 Hertz to 100 Hertz, analog-to-digital converted and stored on a PC for further off-line analysis. Frequency distribution of the signal is between 10 to 30 Hertz in case of physiological tissue.

Results: For malignancies we found a distinct lowering of the frequencies between 4 to 7 Hertz. These results were verified by clinical inspection and histological findings. We also show scarred tissue with small amplitudes and high frequencies and infiltration characterised by high amplitudes and high frequencies.

Conclusion: The proposed non invasive device offers an out-patient method to distinguish different tissues and to prove lesions as malign. Moreover, no (photo) sensitizing agents must be administered. For further analysis methods of chaos theory will be used.

714 PUBLICATION

Serum TNF-α and IL-6 alterations and blood cell counts during the acute phase following head and neck irradiation: An animal study

R.M. Nagler. *Oral Biochemisty Laboratory, Rambam Medical Center and Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*

Purpose: The potential modulatory role of zinc-desferrioxamine [Zn-DFO] on the effects of irradiation [IR] was examined because of its known ability to protect against the damage induced by free radicals mediated by redox-active metal ions.

Materials/Methods: Three groups of male Wistar rats were used: sham irradiated controls; irradiated [15 Gy]; irradiated and treated with Zn-DFO [20 mg/k] one hour prior to IR. During the first two weeks post-IR, body weight and food and water intake were monitored daily, while lymphocytes, segmented neutrophils and white blood cells [WBC] were counted at 10 mins, 4 and 16 hours and 1, 3, 7 and 14 days. Serum TNF-α and IL-6 were obtained at 10 rains and 7 days.

Results: On day 7 post-IR, body weight and food and water intake were reduced by 84%, 96% and 85%, respectively. This resulted in the death of 22% of the animals and was followed by recovery toward the end of the second week At all time points examined, WBC were reduced by 52–74%. On the 7th day, Zn-DFO demonstrated a 33% protective effect against the WBC reduction. At 10 rains post-IR, a 84.8-fold increase of TNF-α but not IL-6 was noted. However, on the 7th day post-IR, both TNF-α and IL-6 levels were increased by 48.5 and 102.5-fold respectively.

Conclusion: The severe cachetic and immunocompromised status of the animals should be considered when performing short-term studies with this model. Nutritional and immunological support is recommended. Further evaluation of the underlying mechanisms of IR-induced leukopenia and cachexia in the animals and the possible implications for humans are warranted.

715 PUBLICATION

Investigation of pentoxyfilline and taxol as a potential radiation sensitizer in C3H mice with FM3A breast tumor

I. Aslay[1], N. Öztürk[2], B. Kurdoglu[3], G. Kemikler[4], S. Özbilen[1], R. Dissç[5]. [1]Radiation Oncology, [2]Medical Oncology, [3]Radiology, [4]Medical Physics, [5]Istatistics, Ist. Univ. Onc. Inst., Istanbul, Turkey

Pupose: Pentoxyfillin (PTX), a methylxanthine derivative, increases the oxygen partial pressure in murine tumors and enhances the radioresponse of the tumors probably by increasing the tumor blood perfusion. Paclitaxel's (TX) ability to arrest cells in the G2 and M phases makes it a potential radiosensitizer. The purpose of present investigation was to elucidate whether the radiation (RT) damage in tumors can be increased with PTX alone or in combination with TX by using growth delay of FM3A tumors in C3H mice as the endpoint.

Methods: Female C3H/HeNBom mice bearing 8 mm FM3A breast carcinoma in their hind legs, were studied in three treated groups that were RT, RT + PTX, RT + PTX + TX and one no treatment (control) group. 50 mg/kg PTX ip. and 60 mg/kg TX iv. were given 15 min. and 24 h before 20 Gy single dose local tumor irradiation respectively. Radiation sensitizer effects were mesured using tumor growth delay (TGD).

Results: There were significant tumor growth delay difference between treatment and control groups. RT, RT + PTX and RT + PTX + TX were more effective on TGD respectively. The enhancement factors were 1.35 in RT + PTX group and 1.85 in RT + PTX + TX group.

Conclusion: PTX and TX gave additive radiopotentiating effect. The present data suggest that these drugs should be considered as a radiation enhancer for clinical radiotherapy.

716 PUBLICATION

Age-related differences in compensation of bone marrow injury after therpeutic irradiation

S.V. Kanaev, S.N. Novikov, L.A. Jukova. *Radiooncology Department, N.N. Petrov Institute of Oncology, St.-Petersburg, Russian Federation*

Purpose: To determine age-related peculiarities of hematopoietic compensation after therapeutic irradiation.

Methods: BM scintigraphy with radiocolloids was performed 1–127 months after the end of radiotherapy (RT) in 69 adults and in 29 children. BM doses ranged from 28 to 45 Gy, irradiated volumes – from one field to total nodal irradiation (TNI). "In-field" BM activity and peripheral expansion of hematopoiesis (PEH) were estimated: from grades 1–2 – no or reduced BM activity to grades 3–4 – partial or full BM recovery; from grades 1–2 -slight or moderate PEH to grade 3 – severe PEH.

Results: During first half a year after RT scintigraphic signs of BM depression were mentioned in 70 of 71 (98%) regions evaluated in adults and in 17 of 17 (100%) – in children. Between 6–12 months after irradiation there were 75% (in 6 of 8 areas) of BM recovery in children and 52% (in 17 of 33 areas) – in adults ($p < 0.05$). Age-related differences in the rates of BM recovery persisted even 13 and more months after RT: grades 3–4 of tracer uptake were detected in 63% (80 of 120) of irradiated regions in adults and in 77% (14 of 18) – in children. PEH was common mechanism of compensation in children. Grade 3 PEH occurred in 12 of 15 patients and appeared even after limited field irradiation. In adults severe PEH was revealed only after TNI and usually appeared 12 and more months after the end of RT.

Conclusion: In children post-RT compensation of hematopoiesis characterised by early PEH and increased rates of "in-field" BM recovery.

717 PUBLICATION

Tumor growth suppression by boron neutron capture therapy with 10B entrapperd PEG-liposome in pancreatic cancer model in vivo

H. Yanagie[1], K. Maruyama[2], T. Takizawa[2], K. Ogura[3], Y. Sakurai[4], T. Kobayashi[4], K. Ono[4], M. Eriguchi[1], H. Kobayashi[5]. [1]Institute Of Medical Science, University of Tokyo, Department Of Surgery, Tokyo; [2]Teikyo University, Department of Pharmaceutics, Kanagawa; [3]Nihon University, Physical Laboratorries, Narasino; Kyoto University Research Reactor Institute, Osaka; [5]Institute For Atomic Energy, Rikkyo University, Yokosuka, Japan

The tumor cell destruction in boron neutron-capture therapy (BNCT) is due to the nuclear reaction between 10B and thermal neutrons. It is necessary for effective BNCT to accumulate of 10B atoms in the tumor cells.

We have reported that intratumoral injection of boronated immunoliposomes can increase the retention of 10B atoms by tumor cells, causing tumor growth suppression in vivo with thermal neutron irradiation. In this study, we prepare a polyethylene-glycol (PEG) binding liposome (DPPC/cholesterol/DSPC-PEG2000) entrapped 10B compound for the application in clinical use of drug deliver sustem. We evaluated the cytotoxic effects of intrveneously injected 10B-PEG-liposome on human pancreatic carcinoma xenografts in nude mice with thermal neutron irradiation. After thermal neutron irradiation of mice injected with 10B-bare liposome or 10B-PEG-liposome, AsPC-1 tumor growth was suppressed relative to controls. Injection of 10B-PEG-liposome caused the greatest tumor suppression with thermal neutron irradiation in vivo. These results suggest that intraveneous injection of 10B-PEG-liposome can increase the retention of 10B atoms by tumor cells, causing tumor growth suppression in vivo upon thermal neutron irradiation.

718 PUBLICATION

Synergistic cytotoxicity by cis-platinum and neutron irradiation in human head and neck squamous cancer cells

H.E. Kim[1], M.A. Krug[2], I. Han[1], J. Ensley[3], H.-R.C. Kim[1,2]. [1]*Wayne State University School of Medicine, radiation Oncology, Detriot, Michigan;* [2]*Wayne State University School of Medicine, Pathology, Detriot, Michigan;* [3]*Wayne State University School of Medicine, Internal Medicine, Detriot, Michigan, United States*

Purpose: Head and neck squamous cancer with poor response to cis-platinum chemotherapy also have poor response to subsequent radiation treatments. The purpose of this study is to investigate mechanisms underlying resistance to cis-platinum and photon irradiation in head and neck cancer cell lines and to study the effects of neutron irradiation on these resistant cell lines.

Methods: On five different head and neck squamous cancer cell lines, cytotoxicity of cis-platinum, photon irradiation, neutron irradiation, cis-platinum with photon irradiation, and cis-platinum with neutron irradiation was examined by clonogenic cell survival assay and sulforhodamine B staining. Neutron-mediated cell cycle regulation and apoptosis were also investigated by Annexin V staining and flow cytometric analysis.

Results: All five cell lines tested were more sensitive to neutron irradiation than photon irradiation. The relative biological effectiveness (RBE) of neutron relative to photon for 10%, 50%, or 90% tumor growth inhibition was 2.3–4.2. Neutron irradiation also enhanced cis-platinum cytotoxicity more efficiently than photon irradiation. G1 and/or G2/M cell cycle arrest was observed following photon and neutron irradiation, but more apoptotic cell death was seen with neutron irradiation than photon irradiation.

Conclusion: Synergistic cytotoxicity of neutron irradiation and cis-platinum suggests a potential clinical application in treatment for head and neck cancer, especially in patients with poor response to cis-platinum chemotherapy.

719 PUBLICATION

Rat model for radiation induced proctitis

S. Kang[1], M. Chun[1], Y. Jin[2], M. Cho[1], Y. Oh[1]. [1]*Ajou Univ. School of Medicine, Dept. of Radiation Oncology;* [2]*Ajou Univ. School of Medicine, Dept. of Anatomic Pathology, Suwon, South Korea*

Purpose: During radiation treatment of pelvic malignancies, most patients experience side effects of proctitis. These side effects can cause treatment interruption that could result in decreased tumor control. This is the study to establish the optimal radiation dose in rat model for clinically compatible radiation-induced proctitis.

Materials and Methods: Female Wistar rats, weighing from 150 to 200 g, were employed. Using 6 MV LINAC, varying radiation doses (0 to 30 Gy) were delivered to the rectum of rat. On the 5th and 10th day after the irradiation, rectal specimens were grossly and microscopically evaluated. From this experiment, we selected 17.5 Gy for radiation-induced proctitis model. Rectal specimens were evaluated sequential gross and microscopic changes by time after irradiation (day 1 to day 14, and week 4, 6, 8, and 12).

Results: There was an increased mucosal damage with increasing radiation dose and a prominent mucosal reaction starting after 15 Gy irradiation. Rats treated with 17.5 Gy showed sequential post-irradiation changes ranging from mucosal edema and mild inflammation to ulcer and fibrosis. These findings were similar to changes found in radiation-induced proctitis of the human. No rats died due to bowel obstruction.

Conclusion: In summary, 17.5 Gy single fraction irradiation to the rat rectum is an ideal model for clinically relevant proctitis where we frequently experience bowel discomfort from swollen tissue but with rare incidence of side effects like mortality or obstruction. Also this study confirmed the dose related radiation injury of the rat rectum as other previous animal models.

720 PUBLICATION

Acute phase response during radiotherapy

M. Cengiz[1], S. Akbulut[1], D. Öztürk[1], E. Özyar[1], I.L. Atahan[1]. [1]*Hacettepe University Faculty of Medicine, Department of Radioation Oncology, Ankara, Turkey*

Introduction: The acute phase response is characterised by changes in the plasma concentrations of a number of liver synthesised proteins, one of which is C-reactive protein (CRP). Existence of these changes in the plasma profile underlies the change in erythrocyte sedimentation rate (ESR). Acute phase response itself is an illness and may be a result of immunological reactions and inflammatory processes. Plasma CRP level is frequently raised in inflammatory bowel disease, shock, trauma, surgery, infection, and myocardial ischemia. This study is designed to determine whether CRP level and ESR increase during radiotherapy (XRT) and whether these rises correlate with acute radiation morbidity.

Material and Method: Between April 1997 and October 1998, fifty-one patients with the diagnosis of endometrial or cervical cancer were treated with surgery and postoperative radiotherapy. Median age at the time of radiotherapy was 52 (26–73). Thirty patients received pelvic XRT, whereas 21 patients were treated by pelvic-paraaortic irradiation. A total dose of 50.4 Gy to the pelvis and 45 Gy to the paraaortic field with conventional fractionation was delivered. Erythrocyte sedimentation rates and CRP levels were studied at the beginning and at the end of XRT.

Results: The median ESR measurements before and after radiotherapy were 40 (8–100) and 43 (10–120) and median CRP levels were 0.59 (0.12–9.8) and 1.73 (0.12–32.2) respectively. The statistical analysis yielded significant rise in ESR and CRP levels at the end of the XRT ($p < 0.001$). The rise was more prominent in patients who were irradiated through pelvic-paraaortic field compared to the patients with pelvic radiation (p:0.005) and (p:0.028) respectively. There was no correlation between clinical severity of acute radiation enteritis and ESR and CRP rise in plasma.

Conclusion: Acute phase response is present during radiotherapy. Statistically significant increase in ESR and CRP levels in large irradiation volumes is observed, as expected due to more radiation- induced inflammation. Radiotherapy should be considered as a cause of increase in CRP level and ESR especially in clinical conditions where acute phase response is important.

721 PUBLICATION

Fundamental studies on the combination of intraoperative radiotherapy (IORT) and a hypoxic cell sensitizer PR-350 for pancreatic cancer

Y. Shibamoto[1], M. Tsujitani[2], T. Kubota[2], K. Kishii[2], M. Takahashi[1]. [1]*Inst. for Frontier Med. Sciences, Kyoto University;* [2]*Pola Chemical Industrial Inc., Yokohama, Japan*

Purpose: To investigate the radiosensitivity of human pancreatic cancer cells and the efficacy of PR-350 (doranidazole) which is being tested in phase I clinical trials in combination with IORT.

Methods: Four human pancreatic cancer cell lines (SUIT-2, PANC-1, BxPC-3 and MIA PaCa-2) and murine SCCVII cells were used. *In vitro,* radiosensitizing effects of PR-350 were investigated under aerobic and hypoxic conditions. *In vivo,* the tumor cells were implanted on the back of Balb/c nude mice, and the hypoxic fraction and the effects of PR-350 were assessed by an *in vivo-in vitro* assay.

Results: *In vitro,* PANC-1 and BxPC-3 were more radioresistant than SCCVII, while SUIT-2 and MIA PaCa-2 were similar in radiosensitivity to SCCVII. The sensitizer enhancement ratio (SER) was 1.25–1.3 at 0.4 mM and 1.4–1.55 at 1 mM in the 4 pancreatic cancer cell lines. These SER's were similar to those observed in SCCVII. The hypoxic fraction was 20% in SUIT-2 tumors and 27% in BxPC-3. The SER of PR-350 was 1.35 at the dose of 250 mg/kg. Investigation with the other tumors is in progress.

Conclusion: SUIT-2 and PANC-1 tumors had a reasonable proportion of hypoxic cells, which suggested the possible benefit of using a hypoxic cell sensitizer at IORT. PR-350 had definite radiosensitizing effect against these tumors.