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537 POSTER

The cribriforme plate on lateral radiographs- a blinded study on the accuracy of radiotherapy planning

S. Gripp, J. Kambergs, M. Wittkamp, A. Saleh. *Universitaetsklinikum Duesseldorf, Strahlentherapie, Duesseldorf, Germany*

Background: Whole-brain irradiation is an integral part in the therapy of several brain tumors and requires coverage of the entire subarachnoid space. Numerous retrospective studies on medulloblastoma revealed frequent recurrences in the fronto-basal fossa above the cribriforme plate. Can the latter be reliably identified on lateral radiographs with sufficient accuracy?

Materials and Methods: The lamina cribrosa was localized by 5 radiation oncologists and 5 radiologists on lateral radiographs of 30 human skulls randomly selected from an anatomical collection. Reference radiographs were acquired under identical conditions except for lead markers pointing to the cribriforme plate and obvious bony edges derived from the ethmoid cells. The targeting deviations were determined by comparing the 300 estimates to the reference radiographs.

Results: In 39% (n=116) the location of the cribriforme plate was correctly estimated within 2 mm. Mislocations of 2-5, 5-10, and > 10 mm were noted in 34% (n=102), 20% (n=61), and 7% (n=21), respectively. Neither speciality nor experience (years of training) had a significant influence on targeting accuracy. If the roofs of ethmoid cells formed prominent bony edges, they were mistaken for the cribriforme plate in 37%.

Conclusions: Lateral radiographs provide ambiguous information to accurately locate the lamina cribrosa in whole-brain irradiation. Localization is significantly impaired by the ethmoid cells.

538 POSTER

Preclinical studies on the combined effect of radiation and S-1: a new oral formulation of 5-fluorouracil on human colon cancer

C. Murayama[1], A. Kamijyo[2], T. Suzuki[2], K. Ishikawa[2], Y. Ohizumi[1], S. Sadahiro[2]. [1] *Tokai University School of Medicine, Radiation Oncology, Isehara, Japan;* [2] *Tokai University School of Medicine, Surgery, Isehara, Japan*

Background: S-1 is a new oral formulation of 5-fluorouracil (5-FU) consist of 1M tegaful, 0.4M 5-chloro-2,4-dihydroxypyridine (CDHP) that inhibits a degradation of 5-FU, and 1M potassium oxonate (Oxo) that regulates the phosphorylation of 5-FU in the gastrointestinal tract, and has shown excellent antitumor efficacy against various murine tumors and human tumor xenografts, compared to the oral tegafur-based antitumor drug, UFT (1M tegafur plus 4M uracil), which is used for chemotherapy or chemo-radiotherapy. The therapeutic effect of S-1 on chemo-radiotherapy was evaluated with human colon xenografts.

Material and methods: KM20C, human colorectal cancer cells, grown in the right hind leg of female BALC/cA nu mice was used when tumors had reached 100-150 mm^3 in size. S-1 was administered orally at a dose of 8 mg/kg/day (as tegaful) for 2 weeks (Day 0-13). 5Gy was given to tumors by 4MV X-rays locally on the first day of experiment (Day 0). Tumor response to the treatments was assessed by calculating relative tumor volume (RTV; mean tumor volume during therapy / mean tumor volume at the start of the drug administration). The anti-tumor effect of the treatment was measured by using the following equation: relative inhibition of the tumor growth (RI, %) = [1-(mean RTV of treated group / mean RTV of control group)] x 100. Apoptosis in tumors was detected by TUNEL assay. The concentration of 5-FU in tumors was determined by HPLC.

Results: The antitumor effect of irradiation was enhanced by the combination of S-1 administration. RI of its combination treatment (5Gy/S-1 group) increased markedly till Day 14 (one day after the last administration of S-1) and this level was maintained for over 30 days. RI for 5Gy group was 6.7%, 18.6%, 29.5% and 41.0% on Day 7, Day 14, Day 30 and Day45, respectively. RI for S-1 group was 21.8%, 33.9%, 28.0% and 16.8%, respectively. RI for 5Gy/S-1 group was 33.2%, 61.4%, 63.8% and 63.9%, respectively. The frequency of apoptosis became maximum at 1 week after 5Gy-irradiation and decreased gradually. This radiation-induced apoptosis was also enhanced by the combination of S-1 administration.Tumor 5-FU levels was found to be various by its administration schedule of S-1. When S-1 was administered after irradiation, tumor 5-FU levels was quite lower than that from oppositely combined schedule: its AUC was decreased to 70%.

Conclusions: These preclinical study suggested that chemo-radiotherapy with S-1 can potentially be used to treatment tumors in place of 5-FU. S-1 administration before irradiation can be expected the higher tumor 5-FU levels and also effective radiosensitization.

539 POSTER

Reproducibility and importance of the bladder status for pelvic irradiation

Z. Cselik, C. Zsolt. *University of Kaposvár, Institute of Diagnostics and Radiation Oncology, Kaposvár, Hungary*

Purpose: The aim of this investigation is to define the impact of the bladder status on internal organ motion and on geometric displacement of defined volumes: organs at risks, gross tumour volume (GTV) and PTV, furthermore on urinary side effects. Moreover to develop a simple way of decrease the physiologic variability and monitoring its reproducibility for conformal irradiation at the pelvic region.

Method: Planning CT of 21 patients has been performed using thermo p lastic mask fixation and belly board with full bladder, t hereafter with empty one. The bladder, rectum, small bowel, GTV and PTV including the elective lymph node regions were indicated and controlled. Using a 3D planning system a conformal dose distribution was planned and evaluated in correlation to the position of the denoted organs. During the course of radiotherapy the patients were educated to come with full bladder and the amount of the urine has been measured after each session. Acute side effects were assessed weekly using NCIC CTC 2.0 toxicity scale.

Results: The V full /V empty = 4,1 ± 2,4 (for bladder). The mean volume irradiated under 80% and 60% isodose curves were near 10 percent higher with empty bladder. The difference was lower comparing the bladder volume irradiated within the 40% isodose curve. The dose homogeneity in PTV was not significantly influenced by the bladder status. The average daily urine amount of 28 patients was 145.8 ml. On the basis of multiple CT and urine measurement the correlation of urine amount to bladder geometry has been established. Interpatient variation was in the range of 0-50ml and 300-650 ml. The adverse events on the bladder were in7% grade3, 3% gr2 and 43% gr1, no toxicity in 47% respectively. The toxicity showed correlation to the urine volume: if the daily average was under 200ml the side effects has increased significantly

Conclusion: In conclusion full bladder is recommended for curative irradiation in the pelvic region. The individual variability of the bladder maximal fullness should be taken into account. The small bladder volume proved to be associated with higher frequency of bladder toxicity. Daily measurement of the urine volume after defined correlation to the organ status leads to better cooperation of the patients and higher quality assurance by conformal pelvic irradiation.

540 POSTER

The informational needs of the multidisciplinary audience attending monthly radiation oncology palliative care rounds at the Toronto Sunnybrook Regional Cancer Centre - needs assessment

E. Szumacher[1], E. Franssen[2], C. Danjoux[1], C. Hayter[1]. [1] *Toronto Sunnybrook Regional Cancer Centre, Radiation Oncology, Toronto, Canada;* [2] *Glaxo Smith-Kline, Statistics, Mississauga, Canada*

Background: Palliative radiotherapy plays a significant role in symptom control in patients with advanced cancer. At the Toronto Sunnybrook Regional Cancer Centre, a Rapid Response Radiotherapy Program was developed to meet patients' needs and a continuing education (CE) program in the form of monthly rounds was developed to meet the educational needs of its multidisciplinary audience.

Purpose: Our primary objective was to evaluate this CE program. The secondary objective was to learn about the informational needs of the multidisciplinary audience attending this CE program.

Methods: A self-administered questionnaire, designed specifically for this project, was used. The questionnaire consisted of two parts. In Part one of the questionnaire, we addressed familiarity, evaluation forms, attendance, and satisfaction level with the educational content and satisfaction with presenting speakers. In part two of the questionnaire, we looked at the educational needs of the multidisciplinary audience and their likelihood of attendance at the sixteen educational topics suggested.

Results: Thirty-two questionnaires were returned out of 50 distributed (response rate 64%). Fifty percent of the respondents were very familiar

with the rounds and 36% were familiar. Fifty-nine percent attended the rounds a few times per year and 28% attended every month. Forty-three percent were very satisfied with the educational content and 54% were satisfied. Sixty-one percent of the respondents were very satisfied with the speakers and 36% were satisfied. Fifty percent of the respondents very rarely returned the evaluation forms and 32% returned the evaluation forms frequently. Lists of the topics for the next year's sessions, as well as the likelihood of attendance, were suggested.

Conclusion: Our Continuing Education program was highly evaluated by the multidisciplinary audience. Several suggestions for continuation and improvement of this program will be discussed at the conference with the detailed analysis of the data.

541 POSTER

The advantage of proton therapy for soft tissue tumours in childhood

B. Timmermann, T. Lomax, G. Goitein. *Paul-Scherrer-Institute, Radiation Medicin, Villigen, Switzerland*

Background: In paediatric radiotherapy, the reduction of dose to all normal tissues is essential to reduce potential late side effects. For children with soft tissue tumours treated with protons at PSI, a comparative treatment planning study has been undertaken comparing these treatments with what could be possible with Intensity Modulated Photon Therapy (IMRT).

Materials and Methods: Seven children were treated with protons at PSI for soft tissue tumours between 1997 and 2002. For each case, IMRT plans have been calculated and compared to the delivered proton dose distributions. Criteria for the comparison were integral dose to the non-target normal tissues, mean doses to selected organs at risk (OARs) and the irradiated volume at 50%.

Results: The median age of the seven children was 12 years (range 7.5-16.1) and indications included two chondrosarcomas, an osteosarcoma, a chordoma, a synovial sarcoma, a rhabdomyosarcoma, and a desmoid tumour. Tumour sites ranged from the upper cranium to the mid-to-lower abdomen. Between 1 to 3 fields were used for the proton plans, and 9, equally spaced, coplanar fields were calculated for all IMRT plans. The total integral dose delivered to the patients by the IMRT plans was predicted to be between 1.5 to 6.1 (mean 3.5) times higher than that for the corresponding proton plans. For selected organs at risk, such as the kidney, spinal cord or brainstem/medulla, the mean doses were between 2.7 to 14.3 (mean 6.4) times higher with IMRT than with the proton plans.

Conclusions: The use of protons has been found to reduce significantly the dose load to OARs and all non-target tissues compared to IMRT. However, IMRT can result in similar levels of high dose conformation. Nevertheless, in paediatric radiotherapy, the reduction of both low and medium dose level could be an important factor in minimizing the risk for secondary cancer and organ deficiencies in young children.

Phase I/Clinical pharmacology

542 POSTER

A multicenter, randomized phase III study on neurotoxicity, safety and efficacy of weekly Paclitaxel infused over 1-h vs. 3-h in patients with advanced solid tumors*

S. Mielke[1], K. Mross[2], T.A. Gerds[3], A. Schmidt[1], W. Lange[4], D. Behringer[1]. *[1] University Medical Center of Freiburg, Department of Hematology & Oncology, Freiburg i.Br., Germany; [2] Tumor Biology Center, Department of Medical Oncology, Freiburg i.Br., Germany; [3] Albert-Ludwigs-University, Department of Medical Statistics and Biometry, Freiburg i.Br., Germany; [4] Johanniter Hospital Rheinhausen, Department of Hematology & Oncology, Duisburg, Germany*

Background: In weekly regimens of Paclitaxel (PAC) the shortening of infusion times to 1-3 hours has lead to a reduction of hematologic toxicity. As neurotoxicity is a frequently observed and often dose-limiting toxicity of PAC we investigated the effects of short infusions on the development of a peripheral neuropathy (PNP) as the primary endpoint.

Study design: Pat. with advanced cancer of different origin (mainly breast, lung, ovary, bladder, head/neck and esophagus) were randomized to a weekly regimen of PAC (100 mg/m^2) infused over 1-h vs. 3-h. PNP was evaluated by a clinical score ranging from 0 (best) to 12 (worst). Pat. increasing with their PNP score to 4-6 (moderate PNP) received a dose reduction (DR) of 25% while those exceeding 6 (severe PNP) were excluded. Pat. with at least SD after six weeks received a second cycle. Kaplan-Meier type curves for the event that PNP score exceeded 3 were calculated. (*This trial was supported in part by investigator-initiated grants from Bristol-Myers Squibb, Munich, Germany.)

Results: Between 03/99 and 01/02 a total of 22 study centers enrolled 121 patients, of whom 92 were assessable for analysis. The probability to exceed PNP score 3 raised from 0.20 vs. 0.30 after one to 0.68 vs. 0.47 after two cycles (1-h vs. 3-h: p=0.66). Grade 3 cases of neuralgia, myalgia or athralgia were predominantly observed after 1-h infusions (22% vs. 5%). Three pat. of the 1-h group exceeded PNP score 6 and were excluded, whereas the number of performed DR was equal (20% vs. 21%). Incidence of grade 3/4 hematologic toxicities was also comparable, while 3% severe HSRs occurred exclusively within 3-h infusions. Median overall survival was longer after 3-h infusions (7.5 vs. 10.4 months; p=0.32) while median progression free survival was nearly equal (3.7 vs. 3.4 months; p=0.68). The objective response rate was 38%.

Conclusions: Although we observed a slight trend towards more neurotoxicity after 1-h infusions we could not find a significant difference in this analysis. The risk to develop a significant PNP increased continuously with therapy duration in both groups, so that it seems to be primarily a question of the cumulative dosage until every patient develops a PNP. Thus, we recommend a continuous evaluation of the PNP score to avoid treatment stops by means of early dose reductions. With respect to the heterogeneity of the tumor entities the survival times and response rates have to be interpreted with caution.

543 POSTER

Tolerability of a novel bone-seeking radionuclide - the alpha emitter radium-223 - in patients with skeletal metastases from breast and prostate cancer

S. Nilsson[1], L. Balteskard[2], S.D. Fossa[3], J.-E. Westlin[4], K. Borch[5], R.H. Larsen[5], O.S. Bruland[3]. *[1] Karolinska Hospital and Institute, Dept. of Oncology and Pathology, Stockholm, Sweden; [2] The University Hospital of Tromso, Dept. of Oncology, Tromso, Norway; [3] The Norwegian Radium Hospital, Dept. of Oncology, Oslo, Norway; [4] Malarsjukhuset, Dept. of Oncology, Esilstuna, Sweden; [5] Anticancer Therapeutic Inventions AS, Oslo, Norway*

Background: Pre-clinical dosimetry and experimental therapeutic studies of the alpha emitter radium-223 ($t_{1/2}$ = 11.4 days) indicate a significant therapeutic potential against skeletal metastases.

Patients and methods: 31 patients (10 breast cancer and 21 prostate cancer patients) have been enrolled in an ongoing phase I trial. In the first part of the study 25 patients was given a single intravenous injection of radium-223 as part of a cohort dose escalating design. Cohorts of 5 patients were followed weekly for 8 weeks. Initial dose level was 37 kBq kg^{-1} b.w. increasing to 74, 130, 170 and 200 kBq kg^{-1} b.w. In the second part of the study, 2 of the patients were given a second injection, resulting in a total dose of 200 kBq kg^{-1} b.w. The tolerability of repeated dosing (100 kBq kg^{-1} b.w. X 2, six weeks interval, or 40 kBq kg^{-1} b.w. X 5, three weeks interval) were studied in 6 prostate cancer patients. The primary objective was to evaluate the safety and tolerance of the drug. Toxicity was monitored using NCI common toxicity criteria and quality of life was assessed (EORTC QLQ-C 30) for all patients. Blood clearance of radium-223 was studied in the initial 25 patients.

Results: Dose-limiting haemotoxicity was not observed in the dose escalating part of the study. Reversible myelosuppression occurred, with nadir 2-3 weeks after injection and recovery during the follow-up period. Neutropenia of maximum grade 3 occurred in 2 of the 25 patients. For thrombocytes, even at the two highest dose levels only grade 1 toxicity was observed. Few adverse events were reported, with nausea as the most frequent event (4 of 5 patients) at the highest dose level. Reversible diarrhoea, grades 1 and 2, responding well to medication, were occasionally observed in all dose groups. Several patients reported pain palliation. For all patients a decline in serum-ALP values was observed. Radium-223 was rapidly cleared from blood; after 24 hours the blood activity level was below 1% of the initial level for all dose groups. To date, no trends towards increased myelosuppression upon repeated dosing have been observed.

Conclusions: Radium-223 was well tolerated by patients with skeletal metastases. Surprisingly low haematological toxicity was observed at potentially therapeutic doses. These results justify further studies to explore the efficacy of radium-223 as a novel targeted internal radioisotope treatment.