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Effects of IORT on thoracic organs

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Purpose: The tolerance of mediastinal structures and thoracic organs to intraoperative radiotherapy (IORT) was investigated in the canine model.

Methods and Materials: Twenty-two adult beagles divided into 3 groups were subjected to a left pneumectomy and IORT (10 MeV electrons) at doses of 20 Gy (N = 9), 25 Gy (N = 4) or 30 Gy (N = 9). IORT was delivered through a 5 cm circular lucite cone encompassing a mediastinal field including the bronchial stump, aorta, esophagus, heart, phrenic nerve, contralateral hilar structures and lung. Clinical monitoring was performed with regular chest X-ray, ECG, bronchoscopy, esophagoscopy and fluoroscopy. From the different treatment dose groups, dogs were electively sacrificed at 1.5, 6, 12 and 72 months with complete autopsies.

Results: There was no bronchial stump dehiscence or acute morbidity. Four dogs developed radiation induced esophagitis (18%), one in the 20 Gy IORT group (11%) and three in the 30 Gy IORT group (33%). There were six IORT related mortalities (27.5%), one esophagoaortic fistula (4.5%), five bronchovascular fistulas (23%); two in the 20 Gy IORT group (22%), two in the 25 Gy IORT group (50%) and two in the 30 Gy IORT group (22%). Histopathological findings in uncomplicated follow-up showed marked myointimal fibrosis in the muscular arteries, submucosal fibrosis of the esophagus and interstitial fibrosis of bronchial and lung tissue especially in the higher dose group.

Conclusion: The mediastinal vascular, bronchial and esophageal structures are relatively sensitive to a dose >20 Gy IORT. The IORT related morbidity found in this study may be lower when the current clinically used IORT doses of 20 or 15 Gy are applied. Further clinical application of IORT in the future treatment strategies for resectable non-small cell lung cancer may be worthwhile to investigate.

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Assessment of tumor microcirculation during fractionated radiotherapy by Gd-DTPA enhanced MR imaging

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Purpose: Recently, we have proposed a novel technique, which allows non-invasive estimation of microcirculatory tumor parameters by dynamic MR imaging, after administration of Gd-DTPA. The objective of our study is, to determine whether this approach is sufficiently sensitive to reveal changes in tumor microcirculation during fractionated radiotherapy.

Methods: The tumor model used in this study is the subcutaneously growing mammary adenocarcinoma AT17 of the C3H mouse. After bolus injection of Gd-DTPA (0.1 mmol/kg Magnevist, Schering, Germany) dynamic T1 mapping with Snapshot FLASH sequences was used to evaluate concentration-time curves for tumor tissue and arterial blood (DMX400, Bruker, Germany). Tumor perfusion and extracellular volume were calculated from these curves by use of a recently developed and verified tracerkinetic model. MR imaging was performed before and in the course of a fractionated radiotherapy with 3 Gy/day, when 15 Gy, 36 Gy, 42 Gy, and 72 Gy were reached.

Results: A significant increase was found for both tissue perfusion and extracellular volume during the course of treatment. At 36 Gy both parameters reached their peak values, and afterwards decreased with on-going therapy.

Conclusion: The technique, applied in this study, may have prognostic value for tumor treatment, especially in combined radio- and chemotherapy.

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Radiation-induced apoptosis of different normal cell populations of rat brain following stereotactic radiosurgery

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Purpose: To investigate the differential sensitivity of neural tissues to stereotactic radiosurgery.

Method: Stereotactic radiosurgery (20–30 Gy) was performed to the base of the brain in male Fisher 344 rats. We studied apoptosis with brain specimen by TUNEL assay and HE stain.

Result: No apoptosis was seen in the un-irradiated brain. Apoptosis increased in the cells of the meninges within a day and ependymal cells within 2 days, and decreased by day 5. A second peak of apoptosis appeared at months 3 and 4 from oligodendrocytes within the white matter, parenchymal neurons as well as ependymal and meningeal cells. Apoptosis gradually decreased within 2 months. Endothelial cell changes were seen mostly at month 7.

Conclusion: Apoptosis appears to affect different types of cells in the brain at different times following irradiation. This may help explain the acute and late radiation changes in normal brain tissue.

711 PUBLICATION

Hypoxic cell sensitizer, PR-350: its radiosensitizing effects on the cells with different p53 status

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Purpose: PR-350, 2 nitroimidazole nucleoside analog, is a promising hypoxic cell radiosensitizer. In this study, the radiosensitizing effect of PR-350 on the cells with different p53 status was evaluated in vitro and in vivo.

Methods: Four fibroblast cell lines; MT158, MT158/neo (contains vectors alone), MT158/wtp53 and MT158/mtp53, established from a p53-knockout mouse, were used in vitro. Cell suspensions with/without 5 mM PR-350 were treated with N_2(5% CO_2) gas for 1 hr and irradiated with 4 MV X-ray. Surviving fractions were determined by a conventional colony formation assay. Human rectal cancer cells, #583, suspected to have the polymophism or deletion on p53 gene, was used for the in vivo test. BALB/cA-nu mice bearing #583 in their legs were irradiated locally with 4MV X-ray. 200 mg/kg of PR-350 was administered 20 min before irradiation. The regrowth delay of the tumors after treatment was obtained.

Results: PR-350 showed the effective radiosensitization on all MT158 cell lines in hypoxic conditions, especially, those on MT158/wtp53 cells was superior to the other three cell lines. PR-350 also produced the radiosensitizing effect on solid human rectal cancer in combination with 10 and 20 Gy of X-ray.

Conclusion: Our results demonstrated that PR-350 exhibited the successful radiosensitization on the cells with different p53 status both in vitro and in vivo.

712 PUBLICATION

Comparison of TGF-beta expressions in lung, live and kidney tiuuses of C3H/He mouse after total body irradiation (TBI)

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Purpose: TGF-beta is one of the main cytokines involved in organ fibrosis and radiation induced fibrotic process is the essential feature of the clinical syndromes following TBI. The expression pattern of TGF-beta, however, does not well known. We evaluated the expression patterns of lung, liver and kidney after TBI in mouse model.

Materials and Methods: C3H/He mouse were sacrificed at 1, 7, 14, 21 and 42 days after TBI of 900 cGy in single fraction. Control group received sham irradiation. The lung, the liver and the kidney tissues are sampled form five mice of each group. We measured tissue TGF-beta levels in milligram of tissue protein using ELISA method. And we fixed remaining tissues for H&E staining and immunohistochemical staining for TGF-beta antibody.

Results: In lung tissue, the degree of septal fibrosis is worsened with time sequence and there was weak staining for TGF-beta at 42 days after TBI. On the measurement of TGF-beta, tissue level of the lung seemed to be peaked at 14 days after TBI. In Liver tissue, There was no definite findings of veno-occlusive disease but one mouse showed perivascular TGF-beta staining at 21 days after TBI. The tissue TGF-beta level, however, peaked at 1 day after TBI. In Kidney tissue, there was no specific finding.

Conclusions: There was no correlation between the pattern of immunohistochemical staining and the amount of tissue expression of TGF-beta. The timing of the elevation of tissue TGF-beta level was different between the lung and the liver.