Radiobiological Studies as a Fundamental Research for Charged-particle Radiotherapy

HIMAC has contracted, and radiobiological studies and clinical trials have started at NIRS in 1994. Following the HIMAC, another 5 accelerator facilities for radiotherapy are working or under construction in Japan. The radiobiological effects of ion-beams are not simple, because of the different radiation quality (ion, energy, velocity, effective charge, LET, track structure, etc.). Damage production, fixation, and modification are different by the radiation quality. In addition, tissues receive ion beams having variety of the energy when the Bragg peak was modulated. Fragments that consist of different ions and energies will be produced through the pass in the tissues. These all phenomena affect the biological effectiveness, and it make difficult to predict the actual biological effects of a beam. Fundamental studies concerning the radiobiological characteristics of ion-beams take a very important place in the radiotherapy and radiobiology with ion-beams. HIMAC cooperative research gave a lot of radiobiological information of ion-beams in the past 7 years. These results together with father studies will be useful in establishment of advanced charged particle radiotherapy.

Genetic analysis can predict prognosis of cervical cancer after radiotherapy
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Our study explored whether p53 status, human papilloma virus (HPV) and LOH on chromosome 3p21.3, 6p21.2, 17p13.1, and 18q21.2 are associated with treatment outcome in 65 patients with cervical cancer after radiotherapy. Tumors and normal DNA were analyzed by PCR for genetic losses at ten polymorphic microsatellite loci. The presence of HPV was analyzed by PCR-based assay using the consensus primers for E6, E7 and L1 region. Mutations of the p53 gene were identified by a single-strand conformation polymorphism analysis. Chromosomes 3p21.3, 6p21.2, 17p13.1 and 18q21.2 were involved in the LOH in 23.1%, 41.5%, 33.8%, and 23.1% of the tumors in this study, respectively. HPV-positive tumors were found in 73.8%, and p53 mutation in 10.8%. The patients with LOH on chromosome 6p21.2 and 18q21.2 survived significantly shorter compared to those without LOH on chromosome 6p21.2 and 18q21.2 in the overall survival (P=0.006, and P=0.007). The HPV-negative patients survived significantly shorter compared to the HPV-positive patients in the overall survival (P=0.01). The results of this study suggest that absence of HPV infection, LOH on 6p21.2, and LOH on 18q21.2 are the most important determinants of outcome of patients with cervical carcinoma after radiotherapy.

Hyperthermic Cancer Gene Therapy

Tumor specific promoters offer an attractive approach to the selective targeting of cancer gene therapy. Tumor cells express heat shock protein 70 (HSP) by in vivo tumor physiological conditions as well as heat treatment (hyperthermia). To investigate the selective usefulness of HSP promoter for cancer gene therapy, hyperthermia and HSV-thymidine kinase (tk) suicide gene combination therapy was examined. In in vitro cytotoxic assays, HSP promoter-oriented tk gene (HSP-tk) transduced cells following heat treatment became 50,000 times more sensitive than HSP-tk transduced cells without heat treatment to ganciclovir (GCV). In in vivo, cancer cell lines implanted in subcutaneous or intraperitoneal mice models were targeted using the HVJ-liposome method. Significant inhibition of tumor growth was observed in HSP-tk transduced tumors following hyperthermia as more than half of treated-mice showed complete tumor eradication. In contrast, non-transduced mice treated with or without hyperthermic showed no prolongation of survival. Immunohistochemical analysis revealed that Fas-mediated apoptosis was involved in the synergistic killing effect of combination therapy. The suicide gene therapy and hyperthermia combination strategy resulted in almost complete tumor regression, suggesting a potentially suitable treatment modality for advanced cancer.