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A new treatment modality for the destruction of solid malignant tumours that utilizes alpha-emitting intratumoral radioactive wires

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Background: Alpha particle irradiation that can be lethal for cancer cells is currently not used effectively in the treatment of solid tumors. We developed a new approach in which tumors are treated with a new type of intratumoral radioactive source that continually releases short-lived alpha-emitting atoms. These disperse in the tumor and deliver a lethal dose over a region measuring 5−10 millimeters in size. We implement this scheme using 228Th to generate wires bearing 224Ra, which, once inside the tumor, release its progeny by recoil. The proposed method was termed Diffusing Alpha-emitters Radiation Therapy (DART). We studied the effect of DART in models of malignant squamous cell (SQ2) and Lewis lung carcinoma (LL/2) in mice.
Methods: Tumor cells were injected subcutaneously to normal Balb/c (SQ2) or C57Bl/6 (LL/2) mice. Tumor bearing mice with 5−10 mm in diameter tumors received a single DART treatment by insertion of a stainless steel radioactive (224Ra) needle (0.3 mm-diameter and 3−5 mm long), having a 224Ra activity in the range of 1.4−81.4 KBq, into the tumor under anesthesia. Animals were monitored for tumor development and for survival.
Results: A single treatment with DART sources of 141 Balb/c mice bearing subcutaneous SQ2 tumors resulted in significant tumor growth retardation, which was dose dependent. DART significantly extended the mean survival time of tumor bearing animals from 14.3±2.6 to 25±5.4 days, and two animals were completely cured. Twenty days after DART the average volume of the treated tumors was 80% smaller than the non-treated tumors in SQ2 bearing mice and 60% smaller in LL/2 bearing mice, Dosimetric studies of the alpha emitters' distribution inside SQ2 tumors revealed doses of 10 Gy up to 5 mm away from the source. Measurements of the liver, kidney, spleen and lungs in DART-treated mice bearing tumors showed local 212Pb activities ranging from 0.05% to 2.5% of the total 212Pb activity released from the wire.
Conclusions: Our long-term goal is to establish DART as a more efficient, safe, and low cost alternative treatment to external radiation radiotherapy. DART can also be combined with surgery, chemotherapy and immunostimulation in order to provide a longer life expectancy, and improved quality of life, and organ preservation.

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Organ at risk atlas-based automatic segmentation for the planning of glioblastoma radiotherapy: validation study for the brainstem

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Background: Radiation therapy (RT) of high-grade glioma requires high dose delivery. Delineation of the target and non-target volumes are thus of paramount importance. This study aims to evaluate the accuracy of an atlas-based automatic segmentation algorithm in defining the brainstem in a large cohort of glioblastoma (GBM) patients.
Materials and Methods: Pre-existing brainstem data of 40 patients with GBM planned for RT were used as the basis in this study. These manually-defined brainstems (MDB) were delineated on the planning CT prior to RT. The brain atlas was generated from a high-resolution diagnostic 16-barett CT dataset. The automatic delineation took the patient images and the atlas images and structures as inputs, and provided the delineation on the patient's image as output. Post-processing image registration was based on level-set segmentation techniques. The volumes of the MDB and automatic-defined brainstem (ADB) were compared.
Results: The median volume of the MDB and ADB were 27.0 (range, 19.3−43.3) and 23.7 (range, 9.5−35.1) cm^3, respectively. The MDB and ADB inter-variability was overall modest: the composite ASB-MSB volume was 20.0 cm^3, but ranged from 8.1 to 29.2 cm^3. This range of values is explained by the substantial inter-variability increase with head-flexion: the median composite ASB-MSB volumes were 22.6 (range, 9.5−29.1) and 27.5 (range, 21.0−35.1) for the flexed and non-flexed patients, respectively. Thus, the median and minimum percentage of composite ASB-MSB volume increased substantially from 72.6−41.3% for flexed patients to 75.2−69.5% for non-flexed patients.
Conclusion: The results indicate that our atlas-based automatic segmentation algorithm provides accurate and reproducible brainstem segmentation for the RT planning of GBM.

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The responses of quiescent cell populations in solid tumors to 290 MeV/u carbon ion beam irradiation in vivo, compared with those of total cell populations

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Background: High-linear energy transfer (LET) radiation gives a higher relative biological effectiveness value for cell killing, a reduced oxygen effect, and a reduced dependence on the cell-cycle, making it superior to low-LET radiation in the treatment of cancer. However, almost all these radiobiological characteristics of high-LET charged particle beams were based on the response of total tumor cell populations as a whole using in vitro cell cultures or in vivo solid tumors. Thus, we clarified the radiobiological characteristics of irradiation with 290 MeV/u carbon ions versus gamma-rays based on the responses of quiescent and total tumor cell populations in vivo.
Materials and Methods: SCC VII tumor-bearing mice received a continuous administration of 5-bromo-2'-deoxyuridine (BrdU) to label all intratumor proliferating (P) cells. Then, they received 290 MeV/u carbon ions or gamma-rays. Immediately or 12 hours after the irradiation, the tumors were isolated and incubated with a cytokinesis blocker, and the micronucleus (MN) frequency in cells without BrdU labeling (= Q cells) was determined using immunofluorescence staining for BrdU. The MN frequency in the total (= P+Q) tumor cell population was determined using tumors that were not pretreated with BrdU.
Results: The difference in radiosensitivity between total and Q cell populations was markedly reduced with carbon ion beams, especially those with a higher linear energy transfer (LET) value, compared with low LET gamma-rays. Potentially lethal damage repair by Q cells was efficiently inhibited with the carbon ion beams, again especially those with a higher LET value, compared with γ-rays. Carbon ion beam irradiation could efficiently reduce the dependency of radiosensitivity on the heterogeneity in solid tumors.
Conclusion: From the viewpoint of controlling solid tumor as a whole, including intratumor Q cells, carbon ion beams, especially with higher LET values, were very useful for suppressing the dependency on the heterogeneity in solid tumors, compared with low LET gamma-rays.

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FDG-PET based planning of limited stage small-cell lung cancer changes radiotherapy fields: a planning study

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Background: The treatment of patients with limited disease small cell lung cancer (LD-SCLC) consists of concurrent chemo-radiotherapy, at the expense of dose-limiting acute esophagitis and lung damage. A straightforward strategy to reduce toxicity is to diminish the radiation fields. In NSCLC, radiation fields could be safely reduced by selective nodal irradiation, based on CT, and even further based on FDG-PET scans. However, in a phase II study in LD-SCLC, we observed 11% of isolated nodal failures. As literature suggests that also in SCLC, PET scan is more accurate than CT in identifying regional lymph nodes, we hypothesized that in patients with LD-SCLC, there would be less geographical miss by using PET scans compared to CT and hence there would be changes in the radiation exposure of normal tissues.
Methods: Twenty-one consecutive patients with LD-SCLC were studied. For each patient, two three-dimensional conformal treatment plans were made where only the pathological lymph nodes were included in the GTV, either based on CT or on FDG-PET scan, both to a dose of 45 Gy in 30 fractions (1.5 Gy BID). From the dose-volume histograms and dose distributions on each plan, the dosimetric factors associated with lung (MLD: Mean Lung Dose; V20) and esophageal toxicity (Dmax: maximal esophageal dose; MED: Mean Esophageal Dose) were analyzed and compared. All values are expressed as mean±SD. Wilcoxon's signed rank test was used to compare differences.
Results: Of the 21 patients, 5 (24%) had mediastinal nodal involvement in different areas on PET compared to CT. In three patients, there were