1398 POSTER

Efficacy of a novel hypoxic cell radiosensitizer PR-350 in the treatment of locally-advanced pancreatic cancer – A placebo-controlled randomized study

K. Karaswa. *Tokyo Metropolitan Komagome Hospital, Radiology, Tokyo, Japan*

Purpose/Objectives: Hypoxia is one of the causes of radioresistance. Many hypoxic cell radiosensitizers such as Misonidazole have been developed but most of them have not continued to be in use mainly because of the toxicity of the drug itself. To reduce the toxicity while maintaining the enhancement ratio, a novel nitroimidazole compound PR-350 was developed and has been in use both preclinically and clinically. Based on the promising phase I data, we used this compound as a phase II placebo-controlled randomized study with the intraoperative radiation therapy (IORT) for locally-advanced pancreas cancer on which hypoxic cells are supposed to pose a problem.
Materials and methods: The eligibility criteria were as follows: age between 20 and 75, PS between 0 and 2, unresectable tumors due to the invasion to the arterial system and/or peripancreatic nerve plexus, tumor diameter less than required for radiotherapy, and absence of organ metastases and/or peritoneal seeding. After laparotomy, a biopsy specimen from each participant was analyzed to confirm diagnosis. Infusions of PR-350 or placebo were performed followed by 25 Gy of IORT. Two weeks following surgery, all patients also received external-beam radiotherapy. Total planned dose of 40 Gy was delivered in 20 fractions. The efficacy of radiotherapy was evaluated using CT examination taken monthly for 6 months.
Results: Between July 1999 and March 2002, 47 patients were enrolled in this clinical trial and received either PR-350 or placebo. Any differences between the PR-350 group (n = 22) and control group (n = 24) were not statically significant. All patients were evaluated, and none of them showed toxicity, with the exception of 1 patient from the control group, and the PR-350 compound was considered to be safe. The committee responsible for evaluating efficacy reported that 47.4% of the PR-350 group showed the effective response, compared with 21.7% of the control group (P = 0.1067, Fisher analysis). At 6 months following treatment, the tumor mass reduction rate in the PR-350 group was significantly improved (P = 0.0274). By the time of the last follow-up in July 2004, 17 PR-350 patients and all control patients group had died of the disease. The median survival period of the PR-350 group was thus 318.5 days and that of the control group is 285.5 days. One-year survival rates of the PR-350 group and control group were 36.4% and 29.3%, respectively. Although the PR-350 group did not demonstrate significantly better short-term survival than the control group, 4 of 22 PR-350 patients were still living more than 3 years after the end of the trial, compared with none of 24 patients from the control group.
Conclusions: For the treatment of locally-advanced pancreatic cancer, the addition of PR-350 to IORT seemed to improve local control and long-term survival. It is expected that this novel compound might well be tested on other tumors on which hypoxia poses a problem such as colorectal cancer, head and neck cancers, and so on.

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A comparison of Gross Tumor Volumes segmented on diagnostic MRI and planning CT with or without post-operative open low-field MRI fusion for 3-D conformal radiotherapy of glioblastomas

D.C. Weber, G. Dipasquale, M. Rouzaud, R. Miralbell. *Geneva University Hospital, Radiation Oncology, Geneva, Switzerland*

Purpose: To assess the post-operative CT-planning gross tumor volume (GTV), with or without open low-field MRI fusion, for the treatment of glioblastomas and compare them to pre-surgery GTVs segmented on a reference diagnostic MRI (GTV*MRI*).
Methods and materials: 10 glioblastoma's patients were prospectively imaged post-operatively using CT and T1-weighted MRI (with Gadolinium) volumetric sequences. MR data with distortion correction were acquired using an open low-field MRI machine (Panorama 0.23 T). Identical patient positioning, using a head mask, was achieved during the post-operative CT and open MRI data acquisitions. GTV were contoured using AcQPlan (Philips Medical Systems, Cleveland, OH) on CT and MRI images and were transferred to Eclipse (Varian, Palo Alto, CA) for 3-D quantitative volumetric analysis. GTVs segmented on CT with (GTV*FUS*) or without (GTV*CT*) open low-field MRI fusion were compared to pre-surgery GTV*MRI*s using the same AcQPlan and Eclipse software.
Results: Reference GTV*MRI*s were usually smaller than planning volumes, with a mean (±1SD) GTV*MRI*, GTV*CT* and GTV*FUS* of 79±33.9, 100.5±44.3 and 107.4±56.4 ml respectively. The mean ration of GTV*CT*/GTV*MRI* and GTV*FUS* /GTV*MRI* were 1.41 (±0.5) and 1.34 (±0.4), respectively. The mean ratio of the GTV*CT*/GTV*MRI* and GTV*FUS*/GTV*MRI* composite volumes were 0.79 (±0.12) and 0.79 (±0.13). Non-overlapping volumes exceeding the reference GTV*MRI* could be substantial, with a mean ratio of 0.64 (±0.45) and 0.55 (±0.39) for GTV*CT*/GTV*MRI* and GTV*FUS* /GTV*MRI*, respectively. More critically, the mean ratio of non-overlapping GTV*CT*/GTV*MRI* and GTV*FUS* /GTV*MRI* not included in the reference GTV*MRI* were 0.23 (±0.1) and 0.20 (±0.08), respectively.
Conclusions: Planning GTVs appeared to be 34–40% larger on average that but not totally inclusive of pre-surgery tumor volumes defined by MRI. In some cases, the CT-, with or without open low-field MRI fusion, volumes were substantially different from references pre-surgery volumes. Open low-field MRI and planning CT fusion could not annihilate all GTV's discrepancies when compared to pre-surgery GTV*MRI*. As a result, the usefulness of post-operative open low-field MR imaging for target definition is questionable.

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Normal tissue sparing with improved conformity of dose to lung tumours using intensity-modulated radiotherapy (IMRT): a theoretical planning study

N. Panakis[1], J. Bedford[2], E. Fernandez[2], E. Nioutsikou[2], S. Ashley[3], M. Brada[1]. [1]*The Institute of Cancer Research, Academic Department of Radiotherapy, Sutton, United Kingdom;* [2]*The Institute of Cancer Research, Joint Department of Physics, Sutton, United Kingdom;* [3]*The Royal Marsden NHS Foundation Trust, Department of Information and Computing, Sutton, United Kingdom*

Aim: To assess the benefit of increasingly complex conformal radiotherapy techniques in terms of reducing normal tissue irradiation in Non-Small Cell Lung Cancer (NSCLC) patients.
Material and methods: We compared 3 coplanar radical radiotherapy techniques in 14 NSCLC patients: 1) conformal 3-field radiotherapy (CRT); 2) conformal inverse planned 3-field radiotherapy using an in-house program, Autoplan (APRT); 3) step-and-shoot IMRT using 5 equispaced beams. The physical parameters compared included: Conformity Index (CI) and Inhomogeneity Coefficient (IC) of the Planning Target Volume (PTV). Lung parameters included the % volume of lung receiving 20 Gy (V_{20}), 13 Gy (V_{13}) and mean lung dose (MLD) relative to the V_{T95} (PTV receiving 95% of the prescribed dose). Oesophageal dose constraints were introduced and the effect on the % volume of oesophagus receiving 50 Gy (V_{50}), maximum dose (D_{max}), mean dose (D_{mean}) and circumferential length of oesophagus irradiated to 40 Gy (LETT 40) were compared. All parameters were tested for normality using the Kolmogorov-Smirnov test and the differences between the planning techniques were assessed by means of the paired t-test or the Wilcoxon signed ranks test.
Results: The improvement in normal tissue sparing with more conformal target coverage is shown in the table. The mean difference in IC between plans of ±0.05 was not statistically significant. Sub-group analysis of 9 patients with central tumours demonstrated an improvement in oesophageal D_{mean} with IMRT compared to CRT (mean difference +3.0 Gy, SD 2.57, p = 0.008 paired t-test).

Region of interest	Parameter	Plan compared	Mean difference	SD	p value	Outcome (ss)
PTV	95% CI	C-A	+0.06	0.13	0.1	
		C-I	−0.11	0.17	0.009	I better than C
		A-I	−0.17	0.14	0.000	I better than A
PTV/Lung ratio	V_{T95}/V_{13}	C-A	+0.43	1.25	0.2	
		C-I	−0.71	1.55	0.1	
		A-I	−1.14	1.57	0.02	I better than A
PTV/Lung ratio	V_{T95}/MLD	C-A	+0.46	2.43	0.5	
		C-I	−1.57	3.16	0.1	
		A-I	−2.03	2.04	0.002	I better than A
Oesophagus	V_{50} (%)	C-A	+0.57	5.23	0.9	
		C-I	+2.42	3.89	0.04	I better than C
		A-I	+1.85	4.96	0.1	

95%CI: CI for the 95% isodose; A: APRT; C: CRT; I: IMRT
SD: Standard Deviation; ss: statistically significant.

Conclusions: IMRT reduces dose to the lung and oesophagus by improving conformity of dose to the PTV. IMRT may facilitate dose escalation and be the optimal radiotherapy technique in concomitant chemo-radiation schedules where radiation-induced oesophagitis is the dose limiting toxicity.