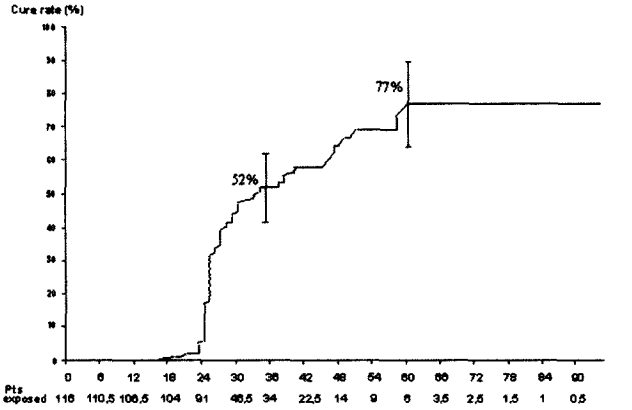
Radiosurgery involved the irradiation of 92% of (109/118) of two targets in 7% of patients (8/118) and of three targets in less than 1% of patients (1/118). All targets were irradiated with a single isocenter. The mean volume of the targets was 7.4cc (0.3-28.3). The mean minimal dose was 17.4 Gy (10-25) and the maximal dose 24.5 Gy (17-36).

Results: The crude and 5-year actuarial rates of cure were respectively 54% (60/112) and 77%. The only independent prognostic factor of cure was volume of the AVM with a cut-off at 7cc (crude cure rate of 67% for <7cc vs. 35% for > or =7cc; p=0.001). No patient died. Permanent complications occurred in 1.7% of patients (2/116) due to radionecrosis or lesion that evolved towards radionecrosis (one hemiparesia and one hemiparesthesia with aphasia). Transient complications occurred in 5% of patients (6/116) (2 cases of hemiparesia, one confusion, one headache, 2 cases of worsened epilepsy). A hemorrhage after radiosurgery occurred in 6% of patients (7/116) with a mean time of 32 months (5-81). Salvage treatment was safe and possible in 19% of uncured patients (10/52) either by use of microsurgery, embolization, a combination of both or a new radiosurgical procedure. Salvage treatment achieved cure in 40% of patients (4/10). All the patients who achieved either a cure (54%: 60/112) or an occlusion of more than 95% of the initial volume of the AVM without cure (20%: 23/112) were free of subsequent hemorrhage. The annual risk of hemorrhage was 1.7% (0.7%-3.4%).

Actuarial rate of Cure of Arterio-Venous Malformation by radiosurgery (Kaplan-Meier)



Conclusion: Our study confirms that radiosurgery is an effective treatment (5-year actuarial cure rate of 77%) of AVM with a low rate of complications. The rate of hemorrhage after radiosurgery is low, nil after cure or with a volume reduction of more than 95%. The rate of adverse-events is comparable to the one expected from the natural history of untreated AVMs.

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The initial clinical experience utilizing an implantable dosimeter for measuring true in vivo radiation dose during external beam radiotherapy

C. Scarantino[1,2], C. Rini[1], T. Carrea[1], M. Aquino[1], R. Ornitz[2], M. Ansher[3].
[1]Sicel Technologies Inc, Morrisille, NC, USA; [2]Rex Cancer Center, Radiaiton Oncology, Raleigh,NC, USA; [3]Duke University Medical Center, Radiaiton Oncology, Durham, NC, USA

Purpose: A reliable *in vivo* method for measuring the dose of radiation delivered at depth does not exist. An implantable telemetric device has been developed to monitor, in real time, the dose delivered at the target site. The final results of the pre-clinical study verified the safety of the implantable device, the lack of adverse events and the ability to measure delivered dose. The purpose of this report is to outline the clinical trial and report on the initial results of the clinical study

Methods and Materials: The implantable device is a product of Sicel Technologies Inc. The pilot study will have 10 patients, with unresectable malignant disease, from any site except brain. The primary end points of this study are to a) assess the safety associated with implantation and movement of the device (adverse events) b) to compare the *in vivo* measured dose with the calculated dose. The device measures 22.0 x 2.5mm and was designed as a permanent implant. As of this submission, 6 patients have been entered onto study. The sites include lung (2), rectal (1), prostate (2) and sarcoma of extremity (1). Following implantation of the dosimeters, standard radiotherapeutic methods were instituted, including simulation and treatment-planning CT scans. A dose point calculation for the predicted dose was determined at the location of the dosimeter end of the device. After the initiation of radiation therapy, the *in vivo* radiation dose was measured daily following each treatment session, and treatment planning CT scans was repeated at 2 and 4 weeks to determine movement of the dosimeters.

Results: The first two patients implanted have completed their planned radiation therapy as of this submission. The remaining 4 patients are in various phases of treatment. The results of the remaining patients will be presented utilizing the same format. There have been no adverse events to date. The results from repeat CT scans did not reveal any significant movement. In the first patient, the average measured dose at the normal tissue was 4% greater than the computed dose during treatment with AP-PA fields, whereas the average measured dose at the gross tumor volume (GTV) was 8.9% less than computed when treating with simple oblique fields. In the second patient, the average percent difference between the measured and computed dose was less than observed with the first patient but was increased by 10% for the final boost.

Conclusions: This report represents the results of the initial pilot study on a permanently implantable *in vivo* dosimeter. The initial results indicate that the device is safe and without associated adverse reaction. There are a number of possible explanations for the variance in radiation dose (e.g. tumor or organ movement), however regardless of the cause the dose recorded by the *in vivo* dosimeter is considered the result of the sum of all the possibilities.

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Plasma Osteopontin (OPN) predicts hypoxia and response to the hypoxic sensitiser Nimorazole in radiotherapy of head and neck cancer. Results from the randomized DAHANCA 5 trial.

J. Overgaard, M. Nordsmark, J. Alsner, J.G. Eriksen, M.R. Horsman. *Dept. of Exp. Clinical Oncology, Aarhus University Hospital, Aarhus, Denmark*

Background: OPN has recently been found to correlate with VHL expression in head and neck cancer, and high level of OPN is found to be associated with tumour hypoxia and expression of HIF-±. The DAHANCA 5 study evaluated the effect of the hypoxic radiosensitizer nimorazole (NIM) and found it to significantly improve the outcome of radiotherapy in supraglottic and pharynx tumours. It is, however, unclear whether all patients may benefit from such hypoxic modification and the aim of the present study was to evaluate in a randomized setting whether OPN had prognostic influence on the outcome as a function of treatment with NIM, and if so, to evaluate whether plasma OPN level was predictive of the response to the hypoxic sensitizer.

Materials and methods: Stored plasma samples from 326 of the 414 originally included patients were available for analysis. Plasma OPN was measured by ELISA (Assay Designs, Inc) and data was evaluated by 5-year actuarial univariate and Cox multivariate analyses. All procedures were as previously described (Rad. Oncol. 46:135-56, 1998).

Results: The 326 analyzed patients were representative of all 414 in the trial and did overall show a significant difference in loco-regional control in favour of NIM with 5-year values of 55% vs. 44%, p=0.05. Plasma OPN level ranges from 12 to 1659 ng/ml. The distribution of OPN values (divided into tertiles) was the same in both treatment arms, and with slightly higher values in N+ patients. Otherwise there was no significant relationship with classical prognostic parameters. Patients with high OPN level had a significantly poorer loco-regional control and survival, but detailed analysis showed that this was only observed in the placebo treated patients, whereas NIM treated showed no relationship between OPN level and outcome. Analyzing the odds ratio for the tertiles as a function of NIM treatment showed an odds ratio for patients with low OPN level of 1.0 (0.5-2.2, 95% cf.l.) and for intermediate of 0.9 (0.4-1.8), whereas for high OPN levels there was a significantly better outcome in the NIM treated patients 0.3 (0.1-0.6), p<0.01. Actuarial analysis confirmed that there was a significant benefit in 5-year loco-regional control (52% vs. 27%), p=0.01and cancer specific survival (45% vs. 25%), p<0.05, if NIM was given to patients with high OPN level. This was confirmed by multivariate analysis which showed no influence of OPN level in NIM treated patients, whereas high OPN level was highly significant for poor outcome in placebo treated patients.

Conclusion: Plasma OPN is an easily obtainable marker and high level is associated with poor prognosis after radiotherapy to head and neck cancer patients. This could be reversed by given such patients with NIM together with radiotherapy. The study is thus indicative of OPN as a predictor for clinical relevant hypoxia and may predict the patients who may benefit from hypoxic modification. OPN measurements should be included in clinical trials evaluating hypoxic modification in order to confirm this hypothesis.

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