EUROPEAN SYNCHROTRON RADIATION FACILITY

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ESRF

Experiment Report Form

The double page inside this form is to be filled in by all users or groups of users who have had access to beam time for measurements at the ESRF.

Once completed, the report should be submitted electronically to the User Office using the **Electronic Report Submission Application:**

http://193.49.43.2:8080/smis/servlet/UserUtils?start

Reports supporting requests for additional beam time

Reports can now be submitted independently of new proposals – it is necessary simply to indicate the number of the report(s) supporting a new proposal on the proposal form.

The Review Committees reserve the right to reject new proposals from groups who have not reported on the use of beam time allocated previously.

Reports on experiments relating to long term projects

Proposers awarded beam time for a long term project are required to submit an interim report at the end of each year, irrespective of the number of shifts of beam time they have used.

Published papers

All users must give proper credit to ESRF staff members and proper mention to ESRF facilities which were essential for the results described in any ensuing publication. Further, they are obliged to send to the Joint ESRF/ ILL library the complete reference and the abstract of all papers appearing in print, and resulting from the use of the ESRF.

Should you wish to make more general comments on the experiment, please note them on the User Evaluation Form, and send both the Report and the Evaluation Form to the User Office.

Deadlines for submission of Experimental Reports

- 1st March for experiments carried out up until June of the previous year;
- 1st September for experiments carried out up until January of the same year.

Instructions for preparing your Report

- fill in a separate form for each project or series of measurements.
- type your report, in English.
- include the reference number of the proposal to which the report refers.
- make sure that the text, tables and figures fit into the space available.
- if your work is published or is in press, you may prefer to paste in the abstract, and add full reference details. If the abstract is in a language other than English, please include an English translation.

ESRF	**Experiment title:** Pilot experiment testing two novel beam configurations in an animal model of malignant brain tumour.	**Experiment number**: MD 275
Beamline: ID 17	**Date of experiment**: from: June 22 to: June 26, 2007	**Date of report**: Sep. 15, 2007
Shifts: 12	**Local contact(s)**: Elke Bräuer-Krisch	*Received at ESRF:*

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Report:

These microbeam radiation therapy (MRT) experiments were using the same preparation phase as MD 131-4, thus making both experiments more viable from both economic as well as time investment for the experimenters. In fact, we have interlaced both experiments in a way that we made the best use of weekdays, on which more support staff was available for new experimental components.

As model were used F98 gliomas in the brains of adult male Fischer rats. This is a highly malignant, very fast growing and metastasizing brain tumour with characteristics very similar of those seen in the malignant human brain tumour glioblastoma multiforme. Previous experiments, using a one-fraction bidirectional irradiation approach with 350 Gy skin entrance dose and ~ 700 Gy deposited in the tumour location had shown that the approach was significantly superior to a hospital-based radiotherapy protocol where one fraction of 10 Gy was given (6MeV). However, other than with the C6 glioma, where we have seen long-term survivors with the above MRT protocol, with the highly aggressive F98 glioma survival was counted in days and weeks rather than months.

Thus, the main component of the MD-275 experiments was to test two new beam geometries for MRT in the hope to achieve better survival in our animal model. The following observations were made and results obtained:

Although all controllable parameters (weight of animals, media used for cell cultures, number of implanted cells) were the same as in previous experiments, we lost a significant number of animals before the scheduled MRT day (day 13 after tumour cell implantation). Although non of the animals died outside the time frame that has been observed for spontaneous deaths before, the percentage of animals dying at days 12 and 13 appeared to be higher than before. As a result, the numbers per experimental group were slightly smaller than planned. However, the numbers were sufficient to give us an indication on the feasibility of the new protocols tested, which was the goal of the experiments.

In both of the new protocols, the TECOMET collimator was used to deliver a total peak dose of 700 Gy was spatially fractionated and delivered in one single therapy session.

New Geometry 1 (NG 1): Delivered were four equal doses through 4 ports (3D star) to the animal being placed on an inclined plane and turned in the horizontal plane at 90° for fraction. Irradiated were 10 animals with tumour and 4 healthy, tumour-free controls.

Of the ten animals with tumour, seven died within 24 hrs after MRT. This is a disproportionally high early death rate and likely due to edema (brain swelling) subsequent to the irradiation added to the already incerased intracranial pressure from the brain tumour. The remaining tumour-bearing animals died on days 19 (x 2) and 32 after MRT. Histological analysis is under way. The healthy control animals are still alive, are continously gaining weight and have not shown any loss of weight. Depending on the results of the histology, future experiments with this protocol might be conducted with antiedematous protection (dexamethasone). Summarizing our experience with this protocol, we have to say that this seems to be a very high risk approach.

New Goemetry 2 (NG 2): Delivered were three equal doses through 3 ports, using a bidirectional protocol with beam arrays crossing at the location of the tumour and adding a vertical dimension. Irradiated were seven tumour-bearing and four tumour-free control animals.

Of the tumour-bearing animals, one died on day 16 after tumour cell implantation (i.e. 3 days after MRT), while the others died between days 34 and 49. This is significantly better than with our protocol used in MD-131.

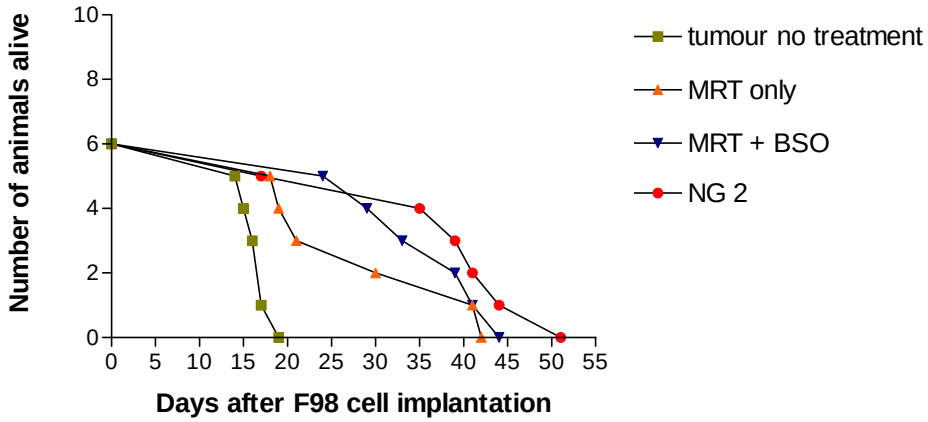

Figure1: Animals treated with our second new beam geometry (NG 2) lived on average significantly longer than those treated with the old MD-131 protocol.

One animal was exclude from the statistics because a major portion of the tumour grew extracranially and thus did not increase the intracranial pressure in the same way as if it would have grown all intracranially (i.e. it would have died much earlier if all the tumour had grown exclusively intracranially).

Unexpectedly, however, about 5 weeks after MRT the healthy, tumour-free controls that had been irradiated with the same protocol, started to first loose interest in drinking water and continually lost weight despite s.c. administration of normal saline and offering of high-caloric fluid nutritional supplements which they eagerly partook of. A loss of alertness, explorative curiosity which is natural to healthy animals and lak of balance were observed and temporary improvement was observed after administration of dexamethasone (antiedematous medication). However, the continous weight loss and neurologic pathology progressed and all four animals had finally to be sacrificed between 9 and 11 weeks after MRT. Histological analysis is pending.

Since the survival of tumour-bearing animals was better with this than with the old MD-131 protocol, we will likely continue to investigate it. The experience with the – free control animals, however, indicates that centering the crossing beams within the tumour tissue is of utmost importance. Therefore, we would like to stress the importance of imaging before therapy a) without the need to change the subject's position and b) with minimal time lapse between imaging and therapy. Although the latter has improved since our experiments in 2006, for which we wish to thank everyone who contributed (especially Drs. Christian Nemoz, Herwig Requardt and Thierry Brochard), it is not yet otpimal for the handling of small animals in an already compromised physical condition.

Finally, we wish to thank Mr. Dominique Dallery for the preparation of our experiments and Ms. Anka Honkimaki for taking care of our animals during the experiments, as well as, Ms. Catherine Massart for her kind support in the cell culture facility. We also would like to thank Dr. Herwig Requard for scheduling our experiments back-to-back in a highly competitive scheduling window. As always, all members of our research team felt well supported and taken care of by the friendly reception at the ESRF.