Thesis points of a Ph.D. doctorial thesis

# PET INVESTIGATION OF RADIATION INDUCED SEQUELAE OF THE SPINAL CORD

*by*

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## Introduction

*In vivo* characterization of radiation induced pathological processes by functional imaging methods has only recently become possible, most promisingly by positron emission tomography (PET). This highly sensitive technique utilizes short-lived, positron-emitting isotopes to label specific molecules that participate in physiological as well as in pathophysiological processes. Tomographic mapping of the distribution of intravenously (i.v.) injected tracers allows precise quantitation of an ever-increasing number of biochemical and/or physiological reactions *in vivo*. The relatively low radiation burden and the noninvasive nature of this particular functional imaging method make it an ideal tool for clinical research and human studies. Our intention was to apply this technique for a more detailed characterization of radiation myelopathy, gathering data heretofore unavailable.

Radiation myelopathy is a rare, but highly feared complication of radiotherapy. It typically occurs following the irradiation or reirradiation of malignant tumors located close to the spinal cord (SC) that are likely to respond to radiation (e.g. malignant lymphomas, seminomas, or certain types of thyroid, laryngeal and nasopharyngeal cancers). It may also be a consequence of application of state-of-the-art, high-dose radiotherapeutic protocols for otherwise incurable tumors (e.g., various forms of pulmonary,

esophageal, head and neck cancer). Myelopathy may affect both the white and the gray matters. White matter involvement is more common, and it usually runs a chronic, progressive, irreversible and relentless clinical course, with only rare instances of even partial recovery from established damage. Thorough research of the available relevant literature-databases on white matter damage has revealed only 7 well-documented published cases of remission. In contrast, regeneration of sensory losses is reported with a relatively higher frequency.

During the past decades, the unfavorable position and external circumstances for radiation therapists plus the often times inadequate instrumentation in Hungary inevitably caused radiation injury at a higher rate compared to the so-called “developed” countries. These cases serve as a pool of patients presenting the clinical sequelae of radiation induced spinal cord damage. Investigation of patients with manifest symptoms of spinal cord injury is a difficult task mostly because their general physical/medical condition. However, it is still feasible when post-therapeutic staging of the disease is required in order to pursue “optimal” – if possible – treatment of a particular disease. Subjects with complete irreversible functional loss fortunately are hard to find and those interested in this special field have to refer to cases, relevant to this type of injuries, reported in the literature.

Although data about the pathomorphology of radiation related damage abound, previous PET studies have provided only limited information on the radiation-induced reactions of the central nervous system (CNS). Data on spinal cord damage are practically not available, since the reported investigations focus exclusively on the pathological changes of the brain, most probably because of the low spatial resolution of PET cameras. In these studies focal radiation necrosis of the brain was visible appearing as a region of decreased [18F]-2-fluoro-2-deoxyglucose (FDG) uptake and reduced blood flow (BF). To our knowledge, regeneration following radiation injuries in the SC has not as yet been studied.

## Aim of the studies

We decided to investigate the various processes ongoing at tissue level by means of PET in patients who suffered from fully or partially reversible radiation injury of the spinal cord. We planned to attempt to relate regional blood flow, glucose metabolism and amino acid uptake of the myelon to clinical signs and symptoms and/or possibly to the results of histological analysis of tissue samples whenever available from these patients in order to get a deeper insight into the mechanisms underlying the restitution of function.

The results of PET imaging done on patients with or without clinical signs or symptoms of myelon damage together with those of the autopsy findings gathered from a similar population offer the chance to possibly describe the pertinent pathologic reactions in greater detail. This approach might also reveal mechanisms that as of now have yet not been perceived as factors important in the recovery process of function.

## Patients and methods

*Patients and radiation protocols*

We have carried out PET studies on a total of 5 patients suffering from different forms of radiation induced damage of the spinal cord in order to complete the information having been obtained by conventional imaging and non-imaging diagnostic methods. One patient represents a case with complete recovery of the spinal cord following a subthreshold dose of irradiation (Patient 1). Two nasopharyngeal cancer patients were investigated due to permanent Lhermitte's sign after radiotherapy. We have reported on PET findings in a patient with partially reversible radiation myelopathy (Patient 4), which were later correlated with autopsy results after her demise. A patient with radiogenic lower motor neuron disease (LMND) was also investigated by PET (Patient 5).

In Patient 1 (a 47-year-old woman) [$^{11}$C]methionine PET had revealed intense tracer accumulation by two lymph nodes measuring about 1 cm in the right parajugular lymphatic region and another tracer-accumulating lesion measuring 1.5 cm in the right hypopharyngeal region. Laryngoscopic evaluation of the hypopharyngeal lesion was consistent with a primary carcinoma ($T_1N_{2b}M_0$) of the right aryepiglottic fold. The PET-demarcated boundaries of the viable neoplastic tissue allowed for a successful partial hypopharyngeal resection and radical right cervical lymph

node dissection. The surgical intervention was followed by external irradiation with 6 MV photons and 8 MeV electrons. The intention was to treat the tumor bed and the bilateral parajugular lymph nodes with a maximum midplane dose of 50 Gy, using daily right and left portals with an angled-down technique (2 Gy/fraction/day, 5 times a week). When a midplane dose of 40 Gy was reached, the field size was shrunk and the spinal cord was no longer exposed directly to the irradiation. The posterior part of the field was boosted by 10 Gy electrons. Thus, the radiotherapy that involved the cervical spinal cord comprised a total dose of 40 Gy, with a calculated BED ($\alpha/\beta = 2$ Gy) of 80 $Gy_2$.

Patient 2 (a 41-year-old uranium miner for the previous 18 years) was diagnosed with a nasopharyngeal cancer ($T_2N_{2b}M_0$) in 1976. He then received telecobalt irradiation with a curative intention, the relevant doses of which are given in Table 1. Besides the total dose and daily fraction dose, the biologically effective dose is indicated, presuming white matter injury in the cervical spinal cord.

A 43-year-old female (Patient 3) had been diagnosed as having stage I extranodal (nasopharyngeal) Hodgkin's disease in 1995 (the histopathology was reviewed and reconfirmed in 2001). She received telecobalt irradiation, with the relevant doses displayed in Table 1.

Table 1. The relevant characteristics of radiotherapy of the investigated patients with Lhermitte's sign

| | **Patient 2** | **Patient 3** |
|---|---|---|
| **Cervical spinal cord total/fraction dose (Gy)** | 48.3/2.3 | 46.2/2-2.2 |
| **BED for the cervical spinal cord ($Gy_2$)** | 103.8 | 94.8 |
| **Tumor total/fraction dose (Gy)** | 60/2 | 41.8/1.8-2 |
| **C2-3 vertebral total/fraction dose (Gy)** | 69/2.3 | 41.8/1.8-2 |

A 36-year-old woman (Patient 4) had been operated on for multifocal papillary thyroid cancer (bilateral subtotal thyroidectomy with lymph node excision; stage $pT_2pN_{1a}M_0$). She received postoperative telecobalt irradiation during 1990. Review of the radiation treatment chart revealed that the radiotherapy was conducted in three series involving 31 fractions during 81 days. Due to miscalculation of the depth of the midplane, and an erroneous daily bilateral application of the dose calculated for a daily unilateral treatment the patient received 3.4 Gy daily fractions during the total of 18 days of the two initial series. During the 13 days of the third series, the daily fraction amounted to 1.7 Gy. In the first two series (with a total duration of 45 days, including the break between them), the field covered the cervical part and the two rostral thoracic segments of the spinal cord. The length of the irradiated part of the spinal cord was 16 cm (the distal segments of which were probably exposed to a lower dose as a consequence of the larger body diameter). During the third series, the field

size was shrunk and the spinal cord was no longer directly exposed. Thus, the radiotherapy involved a maximum spinal cord dose of 61 Gy. During year 2000, the otherwise apparently healthy patient had been complaining for months of short episodes of dyspnoe, but investigations by experts in relevant specialties (oto-rhino-laryngology, neurology and radiation oncology) had not revealed any definite explanatory reason. Later during the same year, she had suddenly lost consciousness resulting from a central respiratory arrest that could not be clinically explained or accounted for. The subsequent 2 weeks of assisted ventilation did not bring about any improvements, while she acquired acute meningitis that eventually led to her death.

Patient 5 (31-year-old male) had been hemicastrated for left-sided seminoma of the most common hystological type in stage $pT_2N_0M_0$ in 1985. Postoperative lymphography revealed no lymph node metastases. During the first postoperative month, the patient had received 1 cycle of chemotherapy. Adjuvant telecobalt irradiation was initiated on the penultimate day of chemotherapy, with the intention of treating the abdominal paraaortic and left parailiac lymphatic regions with a maximum midplane dose of 44 Gy, using anterior and posterior portals daily (2 Gy/day, 5 times a week), resulting in a BED of 88 $Gy_2$.

*Diagnostic imaging methods*

MRI investigations were performed on a 1.5-T system (Magnetom Vision Plus, Siemens, Erlangen, Germany) with a phased-array spine coil. FLAIR and T1-weighted turbo spin-echo sagittal sequences were obtained followed by T2-weighted turbo spin-echo axial scans.

PET investigations were performed with a GE 4096 Plus scanner (General Electric, Uppsala, Sweden), providing 15 two-dimensional sections over an axial field of view of 103 mm. The optimum scanner resolution was 5.5 mm in plane and 6 mm in the axial direction. FDG and [$^{11}$C]methionine studies were made after a 4-h fasting. The doses applied were 5.55 MBq/kg FDG, 9.25 MBq/kg [$^{11}$C]methionine and approximately 2 GBq/scan [$^{15}$O]butanol, and the examinations started from the base of the skull after a lag period of 40, 20 or 0 (immediately) min. following the administration of the tracers. For numerical comparisons, standardized uptake values (SUVs) were determined in the axial plane of the PET images by placing regions of interest (ROIs) covering the spinal cord between the appropriate vertebral bodies to characterize both irradiated and nonirradiated segments.

*Electrophysiological studies*

Electrodiagnostic testing included electroneuronographic (ENG) and electromyographic (EMG) investigations. ENG was performed on the

peroneal and posterior tibial nerve bilaterally to look for diminished peripheral motor or sensory conduction velocity by measuring the mean velocity of conduction and comparing it to the normal value.

EMG was performed on the right and left quadriceps muscles, the anterior tibial muscle and the triceps muscle on the calf to look for signs of peripheral neurogenic lesion and fibrillation.

*Radiobiological and pathological methods*

Four sets of different studies were performed to check whether any kind of an individual high radiosensitivity might have played a role in the development of radiation-induced spinal cord injuries. First, a primary fibroblast cell culture had been established from a skin biopsy and then, in a clonogenic assay, fibroblasts were irradiated with different doses of γ-radiation, and the survival rates were compared with the clonogenic survival of primary fibroblast cultures isolated from foreskin samples from 6 healthy children. Second, in a single cell electrophoresis (comet) assay, whole blood had been irradiated with 2 Gy of γ-radiation followed by a comet analysis either directly after the irradiation to measure the initial DNA damage, or 4 hours later to allow time for DNA repair and determination of the residual damage. Data evaluation was carried out using the Komet Analysis System software package (Kinetic Imaging Ltd, UK). The initial and the residual DNA damage in the lymphocytes of the patients were compared with the

results obtained on 43 samples collected from healthy individuals. Third, the spontaneous and the 2 Gy γ-irradiation-induced micronucleus frequencies were measured in a micronucleus assay and compared with controls. Finally, the presence of chromosome aberrations was checked after in vitro irradiation of peripheral blood samples and compared with controls.

Histopathological analysis included Woelcke myelin staining for the demonstration of demyelination as well as for the presence of thin remyelination at the edges of the demyelinated areas. Axonal loss was evaluated by Bielschowski's method. We searched for the signs of motor neuron degeneration using Nissl's staining. Hematoxylin-eosin (HE), Periodic acid-Schiff (PAS), trichrom, van Gieson and Ag stained sections were analyzed for signs of vascular-wall alterations.

## Results and discussion

*PET studies on the recovery of the spinal cord following a subthreshold dose of irradiation*

A very low, background FDG accumulation was observed in the cervical spinal cord of Patient 1 (mean SUV: 0.84), before the initiation of radiotherapy. An increased FDG uptake was measured 3 months after radiotherapy (09/1998, mean SUV: 1.69), which was followed by a decline, as measured 8 months later (02/1999, mean SUV: 1.21). The FDG accumulation in the irradiated segments of the spinal cord decayed to a level very close to the initial value 46 months after the irradiation had been completed (04/2002, mean SUV: 1.11). The simultaneous [$^{15}$O]butanol uptake results demonstrated a pattern of perfusion changes similar to those observed in the FDG studies. The patient had an extremely low [$^{11}$C]methionine uptake within the nonirradiated and irradiated segments of the spinal cord and this has not changed during the clinical course (the mean SUVs were between 0.35 and 0.25). The bone marrow uptake disappeared from the irradiated vertebral bodies C2-D3 (C1 has practically no body).

In the fourth year of the clinical course, radiobiological investigations were performed. The fibroblasts of the patient displayed a slightly increased radiation sensitivity relative to those of the healthy

controls. In the comet assay, no essential difference was found between the DNA repair capacity of the patient's lymphocytes and those of the controls.

An elevated glucose metabolic rate can be concomitant with cell division or with inflammatory processes that may comprise or be part of the pathological responses of the CNS to ionizing radiation. Demyelination (due to the death of oligodendrocytes and glial progenitor cells) is one of these pathological processes and it inevitably results in consecutive gliosis and astrocytosis (Type 1 lesion). Both cellular reactions require extra energy consumption. It is generally accepted that energy-demanding remyelination is a *sine qua non* prerequisite for functional regeneration. Vascular (Type 2) lesions include endothelial cell damage, preferentially in capillaries and venulae, which is usually accompanied by a chronic inflammatory reaction involving mononuclear cells (lymphocytes, mainly T cells, macrophages) and microglia, simultaneously with fibrinoid necrosis of the vascular wall. This so-called radiation vasculitis results in an increased FDG uptake. In addition to the white matter reactions, gray matter sequelae may also occur in the anterior and posterior horns of the spinal cord, and it is not clear whether or not this may contribute to the elevated glucose metabolic rate.

Thus, the temporarily increased FDG uptake after radiotherapy may be related to subclinical, transitory demyelination and vascular

inflammation, triggered by a not too high dose of irradiation. The background level of [$^{11}$C]methionine accumulation in the spinal cord segment exposed to radiation can be regarded as strong evidence against intensive cell proliferation or intense inflammation. The almost complete disappearance of the temporary increase in the FDG uptake of the irradiated spinal cord region by the 44th month is in accord with the finding that the monkey spinal cord virtually completely recovers from radiation damage in 3 years.

*PET characterization of partially reversible radiogenic spinal cord injuries*

*A. PERMANENT LHERMITTE'S SIGN*

In a clonogenic assay, fibroblasts obtained from Patient 2 displayed much higher radiation sensitivity than those of healthy controls, while radiation sensitivity of the fibroblasts from Patient 3 was normal. In the comet assay, no essential difference in DNA repair capacity was found between the patients' lymphocytes and those of the controls.

MRI evaluations did not reveal any pathological signs either in Patient 2 or 3 twenty-five and 7 years postirradiation, respectively despite the fact that conditions were completely appropriate to demonstrate a pronounced demyelinated state of the spinal cord, would that have been the case.

In Patient 2 and 3, FDG PET examinations indicated an increased uptake in the irradiated cervical spinal cord (mean SUVs 1.56 and 1.60, respectively) as compared with the nonirradiated segments (mean SUVs 0.60 and 0.84). [$^{15}$O]butanol PET investigation likewise revealed an increased blood flow in the region of the spinal cord that had previously been exposed to the radiation field, but [$^{11}$C]methionine PET examination resulted in a negligible tracer uptake for both the irradiated (mean SUVs 0.36 and 0.31, respectively) and the nonirradiated segments (mean SUVs 0.50 and 0.40). No [$^{11}$C]methionine uptake was detected in the bone marrow of the vertebral bodies C1- C3 irradiated by high doses (69 Gy and 41.8 Gy, respectively).

The most noteworthy features of the clinical courses of the patients were (i) complete clinical recovery from the motor injuries (Patient 2), (ii) the incomplete regeneration of the sensory symptoms (Patient 2); and (iii) the permanency of the LS (both cases).

Radiation damage brings about alterations in the molecular structure of the axon membrane and demyelination is one of the most marked changes. After loss of the myelin sheath, the segments between the nodes of Ranvier, harboring sodium channels in low density, are exposed to the interstitial fluid. Demyelization of the axons results in a reduced speed of the action potential conduction. It is documented that a higher than

normal density of sodium channels may restore conduction in some chronically demyelinated axons. It is fair to speculate that the modified molecular structure and altered conducting mechanisms of these internodal segments give rise to extra energy requirements. This is most likely related to a larger perturbation of intraaxonal ion concentrations during the propagation of the action potential as a consequence of the larger number of sodium channels involved in conduction. The pumping-out of extra amounts of intracellular sodium against a concentration gradient can be accomplished only at the cost of extra energy consumption.

The existing close coupling of glucose utilization to tissue perfusion in the spinal cord with its restored conduction provides a full explanation for the observed increased blood flow in the radiation-damaged segments with their reconstituted function and increased glucose metabolism. Such an interrelationship (i.e., the flow and glucose metabolism coupling has become an "axiom") is basically the same as that already proved for the brain.

*B. INCOMPLETE SPINAL CORD TRANSECTION*

In Patient 4 native T1 weighted MRI images revealed atrophy throughout the length of the spinal cord, reflecting axonal loss and Wallerian degeneration; it was especially marked in the upper two-thirds of the thoracic region.

The first PET examination, during the 6th year of the clinical course, indicated an increased FDG uptake in the cervical spinal cord. Eight months later, a second FDG PET examination revealed an unchanged longitudinal extent of the increased uptake zone, with an irradiated to non-irradiated spinal cord FDG uptake ratio of 2.6. During the 8th year of the clinical course, [$^{15}$O]butanol PET examination showed an increased blood flow within the irradiated spinal cord segment, but [$^{11}$C]methionine PET examination indicated a negligible tracer uptake for both the irradiated and the non-irradiated segments of the spinal cord.

Although a marked improvement occurred in the sensory losses, the most noteworthy feature of the clinical course of this patient was the partial recovery of the motor impairments attributed to the white matter injuries.

The explanation of the PET-findings could be the same as proposed for the cases with permanent Lhermitte's sign. Further support was acquired from the detailed post mortem pathologic analysis of the spinal cord.

*Autopsy findings in partially reversible radiation myelopathy*

Besides acute purulent meningitis throughout the CNS, the autopsy of Patient 4 did not reveal signs of any other illnesses. The histopathology verified the macroscopically diagnosed acute purulent meningitis, revealing

extensive perivascular and meningeal polymorphonuclear neutrophilic infiltration all over the entire CNS. There was no indication of chronic inflammation, neither that of astrocytosis, gliosis nor an accumulation of mononuclear cells was detected. The cervical portion of the spinal cord that had received the miscalculated high dose of radiation displayed a pronounced, bilateral loss of myelin and axons mainly within the lateral and to a lesser degree within the posterior columns. A few thinly remyelinated sheaths were present at the edges of the demyelinated areas. Moreover, bilateral, extensive damage to neurons was also observed, most markedly among the motor neurons of levels C1 and C2, and was practically identical on both sides. The larger and smaller arterioles and venules of the irradiated spinal cord were intact, but the walls of some capillaries exhibited thickening. Telangiectasia was not observed. Below the irradiated cervical spinal cord segments, bilateral, secondary pyramidal tract degeneration was obvious.

*PET findings in radiogenic lower motor neuron disease*

Magnetic resonance imaging (MRI) of Patient 5 patient failed to show any pathological signs. The FDG PET examination indicated an increased uptake within the lower thoracic and lumbar spinal cord, while [$^{11}$C]methionine PET investigation resulted in no tracer uptake in either the irradiated or the non-irradiated segments of the spinal cord. No methionine

uptake was found in the D10-12 and lumbar vertebral bodies, in accordance with the boundaries of the radiation portal. [$^{15}$O]butanol PET examination did not provide interpretable results because of the high blood flow in the abdominal large vessels.

The radiation sensitivity of the fibroblasts of the LMND patient was in the same range as that of the controls. In the comet assay, no essential differences in the initial damage were detected and the DNA repair was complete after 4 h. In the micronucleus assay, the spontaneous micronucleus frequency was slightly higher in the LMND patient than in historical controls. After irradiation with 2 Gy γ-radiation, the micronucleus frequency was elevated to 236/1000 cells, which was in the same range as the controls.

The noteworthy feature in the clinical course of this patient was the partial recovery from LMND. Recovery from grey or white matter damage causing motor deficit is a rare event: only 8 and 7 well-documented cases, respectively, have been published.

Considering the above we can conclude, that in this case again the changes related to the restoration of the conduction on demyelinated axons might be responsible for the elevated energy demand, hence the increased FDG uptake.

## Conclusions

We can summarize the results of our investigations as follows. Radiation myelopathy usually runs a chronic, progressive, irreversible and relentless clinical course, with only rare recovery from established motor sequelae. The cases we have reported on, that represent at least partially reversible radiation injury, have common features from the point of view of tissue metabolism detectable with PET. However, with the help of the other investigational methods applied, different (patho-)physiological processes could be identified in the background of these phenomena.

All patients exhibited increased FDG accumulation indicating elevated levels of glucose metabolism in those spinal cord segments that had been included in the radiation fields. Regional tissue perfusion measurements with [$^{15}$O]butanol showed parallel results, excluding severe deterioration of microcirculation. The increased tracer uptake observed can properly be attributed to a higher energy demand, since glucose is the primary fuel to nervous tissue. The need of this extra energy could not be attributed to cell proliferation on the basis of either the anamnestic data or the pathologic findings, and was further supported by the results of [$^{11}$C]methionine PET measurements.

The restoration of axonal conduction, reflected by the improvement of the clinical symptoms, suggests that an alternative

conduction mechanism (continuous impulse propagation) takes place in order to overcome the blockade caused by the loss of myelin sheath. This implies an elevated number of $Na^+$-channels resulting in more effective $Na^+/K^+$-pump function, hence higher ATP demand.

As a summary, we can conclude that PET investigation of radiation induced myelopathies of different severity provides new insights into the functional recovery of the cord suggesting mechanisms for the restoration of conduction not perceived so far.

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