in order to improve the Treatment Planning Systems (TPS) software, so to properly take into account not only the normal tissue toxicity in the target region, but also the risk of late complications in the whole body [1,2]. All the aforementioned issues underline the importance for an experimental effort devoted to the precise characterization of the neutron production gaining experimental access both to the emission point and production energy.
The technical challenges posed by a neutron detector aiming for high detection efficiency and good backtracking precision will be addressed within the MONDO (MOnitor for Neutron Dose in hadrOntherapy) project. The MONDO main goal is to develop a tracking detector targeting fast and ultrafast secondary neutrons.
The main interaction mechanism of fast and ultrafast neutrons in plastic scintillators is the elastic scattering with hydrogen nuclei. In case of double elastic scattering events, if both protons recoil are measured, the neutron energy and direction can be reconstructed. The tracking and energy resolution achievable on the two recoiling protons drive the neutron energy and angular resolutions. The tracker is than composed by matrix (10 x 10 x 20 cm^3) of squared scintillating fiber of 0.250 mm). The fibers are used at the same time as target for the elastic n-p scattering of the impinging neutrons and as active detector for the recoiling protons. The light produced and collected in the fibers will be amplified using a triple GEM [3] and acquired using CMOS Single Photon Avalanche Diode arrays [4].

The neutron tracker will measure the neutron production yields, as a function of production angle and energy, using different therapeutical beams (protons, 12C ions and possibly 4He and 16O ions).
The MONDO project and the preliminary test of the different components will be presented.

Keywords: Tracking detector, Neutrons, Particle Therapy

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Modeling the effect of symmetrical division of cancer stem cells on tumour response to radiation
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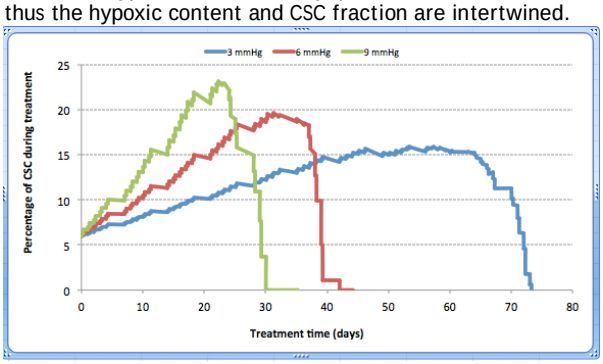
Purpose: A growing body of evidence on cancer stem cells (CSC) relates their presence in tumours to poor treatment outcome. Symmetrical division of CSC during therapy is a key factor that contributes to repopulation and treatment failure. However, the literature lacks quantification of the CSC fraction and their division pattern. Head and neck cancers (HNC) are challenging due to high hypoxic content and repopulation ability by CSCs. The aim of this work was to quantify the symmetrical division of CSC in a hypoxic HNC model treated with hyperfractionated radiotherapy and assess tumour response as a function of the interplay between CSC and the hypoxic fraction.
Methods: A Monte Carlo technique was employed to grow a HNC consisting of CSC, differentiated and quiescent cells. For a biologically realistic growth, the initial symmetrical division probability of CSC was 1.9%, leading to a pre-treatment CSC population of 5.9%. The model considers various hypoxia levels as a function of the mean partial oxygen tension, from 3mmHg to 10mmHg. CSC radioresistance was established according to literature [1] and adapted for HNC.
Results: Initial CSC fraction changes during treatment due to repopulation, radioresistance and hypoxia. Figure 1 shows the variation of CSC fraction during therapy for three hypoxic scenarios. The figure shows that in mildly hypoxic tumours (9 mmHg) the fraction of CSCs during treatment overtakes the fraction of CSC in severely hypoxic ones (3 mmHg). It nearly appears that hypoxia keeps the CSC subpopulation under control. This behaviour is due to the fact that in well-oxygenated tumors CSCs are the most resistant subpopulation and they outlive non-stem cells, while in hypoxic tumors there are hypoxic resistant subpopulations as well as CSCs, thus the hypoxic content and CSC fraction are intertwined.



While hyperfractionation (1.2Gy in 70 fractions) is likely to be the most optimal radiotherapy schedule for advanced HNC [2] the model shows that if repopulation occurs via symmetrical division of CSCs with a probability greater than 5%, radiotherapy as a sole agent is not efficient for hypoxic HNC (table 1). However, oxic HNC benefit from hyperfractionation even for larger probabilities of symmetrical division, thus an overall dose of 84Gy in two 1.2Gy daily fractions is effective to overcome repopulation.
Conclusions: Quantitative evaluation of CSCs and hypoxia are crucial for designing successful treatment regimens for resistant subpopulations.

	Probability of CSC symmetrical division	1.9%	5%	10%	20%	30%
Number of 1.2Gy fractions for complete tumour eradication	*Oxic HNC*	48	49	52	58	70
	Mildly hypoxic HNC	52	53	56	65	81
	Moderately hypoxic HNC	74	78	86	117	210
	Severely hypoxic HNC	131	154	199	> 250*	

* The shaded areas correspond to clinically unfeasible situations

Keywords: cancer stem cell; hypoxia; hyperfractionated radiotherapy

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Hadron minibeam radiation therapy: feasibility study at the Heidelberg Ion-Beam Therapy Center (HIT)
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Purpose: Despite recent advancements in radiotherapy and radiosurgery, significant limitations remain. Hadrontherapy, which has been in clinical use for more than 15 years, has shown remarkable effectiveness. However, it still could benefit from a lower impact on non-targeted tissues to allow its administration at higher doses. This is the reason why we propose a new approached called hadron minibeam radiation

therapy (hadron MBRT). The technique is based on the well established tissue-sparing effect of arrays of parallel, thin or small beams, observed in studies performed with synchrotron radiation [1-2]. In parallel, significant tumor growth delay was observed in highly aggressive tumors by using interlaced irradiations [1-3]. Hadron MBRT combines the advantages of MBRT with the high dose conformability and the remarkable biological effectiveness of hadrontherapy. This novel strategy might guarantee tissue recovery and reduce the side effects of radiation in healthy tissues. The main goal of this study was to explore this new approach from a dosimetric point of view and to verify its technical feasibility at a clinical center (HIT, Germany). In particular, carbon and oxygen minibeams were studied.
Materials/methods: Carbon and oxygen minibeams were generated through a tungsten multislit collimator with line apertures of 700 µm separated by 3500 µm. Scanned 12C and 16O pencil beams were used to cover a given irradiation field size (1x1 cm2) and a spread out Bragg peak (SOBP) region of 5 cm at 8 cm-depth in water. Radiochromic films (EBT3) were placed at several depths in a solid-water slab phantom to evaluate dose distributions. Quenching effects of these films were also assessed and results were accordingly corrected.
As a figure of merit, the ratio between the central dose of one minibeam (peak dose) and the dose in the middle of two consecutive beams (valley dose) was evaluated. This magnitude, named peak-to-valley dose ratio (PVDR), is a very relevant magnitude in such spatially fractionated techniques [4].
Results: The measured lateral dose profiles in carbon and oxygen MBRT consisted in a pattern of peaks and valleys, which prove the technical feasibility of this approach. This first dosimetric study showed PVDR values around 10-20 in the first centimeters of the phantom. PVDR values progressively decrease up to around 5 at 8-cm-depth. These PVDR values are in the order of the ones obtained in x-rays MBRT, for which biological effectiveness has already been proven.
Conclusions: This is the first exploratory study that experimentally proves the technical feasibility of hadron MBRT at a clinical center. The PVDR values obtained showed the potential of this radiotherapy approach, which might allow reducing side effects in the healthy tissues. Animal experiments are warranted.

Keywords: minibeam radiation therapy, hadron therapy, experimental dosimetry

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Infrared study of the biochemical effects in glioma cells induced by x-rays and Gd nanoparticles: first studies at SESAME synchrotron (Jordan)
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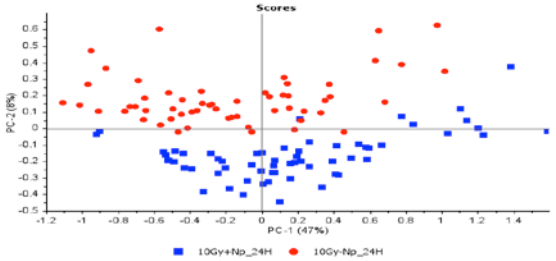
Purpose: One strategy to improve the clinical outcome in radiotherapy (RT) is to increase the dose effects in the tumor. This can be achieved by using specific nanoparticles (NP). Numerous studies have shown an enhanced effectiveness of tumor cell killing when NP were associated to irradiation [1-3]. However, the mechanisms of action are not yet clear. In addition to the damage due to a possible local dose enhancement, the interaction of NP with essential biological macromolecules could lead to changes in the cellular function, such as cell arrest at radiosensitive phases [4]. These effects, which could be amplified with a subsequent irradiation, might increase their anticancer effectiveness. Along this line, in this study we used F98 glioma rat cells as an *in vitro* model to evaluate the intracellular biochemical changes induced by x-ray irradiations in combination with Gadolinium NP by using Fourier transform infrared microspectroscopy (FTIR). FTIR allows *in situ* chemical structure determination of intracellular biomolecules. In addition, this technique has significantly contributed to study apoptosis, as well as cell cycle and cell death modes.
Materials/methods**:** FTIR measurements were performed using the internal source of infrared radiation at SESAME synchrotron (Jordan). Principal Component Analysis (PCA) was performed to show the variances between the different sets of spectra.
Results: Noticeable spectra alterations in the presence or absence of NP were detected in the proteins, DNA and lipids regions, indicating changes in the cellular function (even in the absence of radiation). In particular, biochemical changes related to apoptosis were detected. These include a shift toward the low wavenumbers in the amide I and II bands, relative amplitude changes in the CH2 and CH3 stretching modes, along with DNA chromatin condensation indications [5]. The figure below shows an example of PCA analysis in the DNA region of the infrared spectral range in the presence and absence of NP for a dose deposition of 10 Gy.



Conclusion: This is one of the first research studies performed at the Emira laboratory of the SESAME Synchrotron (Jordan). This infared work provides new insights on the biochemical effects induced by the combination of radiotherapy and nanoparticles, for which the full mechanisms of interaction are not well known up to now. Results will be discussed in relation to cell viability studies.

Keywords: Fourier Transform Infrared Microspectroscopy, radiotherapy and nanoparticles, F98 glioma cells.

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Construction and first tests of a PET-like detector for hadrontherapy beam ballistic control
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We present the first results obtained with a detector, called Large Area Pixelized Detector (LAPD), dedicated to the beam ballistic control in the context of hadrontherapy.
The purpose is to control the ballistics of the beam delivered to the patient by in-beam and real time detection of secondary particles, emitted during its irradiation. These particles could be high energy photons (γ prompt), or charged particles like protons, or 511 keV γ from the annihilation of a