

Full clinical exploitation of the superior dose conformality promised by ion beam therapy could greatly benefit from in-vivo and non-invasive verification of the dose delivery, to monitor safe application of the planned treatment and enable adaptive strategies in case of deviation between actual and intended irradiation. Indeed, detection of the surrogate transient pattern of tissue  $\beta^+$ -activation (mainly  $^{15}\text{O}$  and  $^{11}\text{C}$  with half-lives of 2 and 20 min, respectively) induced by therapeutic proton irradiation was envisaged since the late 1970s as a potential mean to visualize the treatment delivered to the patient. However, about 30 years elapsed before Positron-Emission-Tomography (PET) verification of proton therapy could be investigated in thorough clinical trials. This was mainly due to 1) the technical challenges for realization of dedicated in-beam PET scanners integrated into clinical treatment units and 2) the methodological limitations (especially from co-registration issues) of post-radiation imaging using commercial standalone PET devices.

The recent advent of commercial combined PET/CT (Computed-Tomography) scanners helped overcoming the major drawbacks of post-radiation PET imaging alone, due to the availability of the additional CT information for co-registration with the planning CT. To date, first clinical trials have been reported for about 50 patients scanned with PET/CT for up to 30 min starting up to 20 min after proton irradiation at the Massachusetts General Hospital (MGH), Boston, the National Cancer Center (NCC) of Kashiwa, Japan, and the University of Florida, Jacksonville. This presentation will give emphasis to the initial clinical experience from MGH. This is so far the only proton center addressing the feasibility of range verification by comparing the PET/CT measurement with a detailed Monte Carlo modeling of the expected activation, as done for in-beam PET of >400 carbon ion patients at the GSI Helmholtzzentrum für Schwerionenforschung Darmstadt.

Despite the promising results mainly achieved for head-and-neck tumour cases, post-radiation PET/CT imaging suffers from several limitations including the loss/degradation of the activity signal due to physical decay and biological washout in the time elapsed between irradiation and imaging, the need of repositioning the patient at the imaging site and the internal organ motion during the prolonged PET scan. Improved performances of PET applications are expected for shorter delay times between irradiation and imaging. Therefore, recent developments are exploring the clinical advantages of novel in-beam and in-room PET detectors at NCC and MGH, respectively.

The so far accumulated/ongoing clinical experiences in proton therapy are restricted to passive beam delivery. However, as shown for  $^{12}\text{C}$  therapy and proton phantom studies with stationary targets, PET verification is also applicable to the emerging scanned ion beam techniques. These are very sensitive to organ motion. Therefore, this presentation will also address the potential benefits of time-resolved imaging, as supported by first phantom experiments for 4D in-beam PET verification of carbon ion beam tracking at GSI.

**Learning Objectives:**

1. Review the motivation and principles of PET/(CT) verification of proton therapy
2. Underline merits and limitations of the current clinical implementations of post-radiation imaging
3. Provide an overview on the latest/ongoing developments aiming at improved clinical performances