A nano-microdosimetric characterization of a therapeutic carbon ion beam at CNAO

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ABSTRACT

A nano-microdosimetric tissue-equivalent proportional counter (TEPC) capable of measuring microdosimetric spectra of ionizing radiation in the range 500 - 25 nm was designed, constructed and deeply characterized in order to fill the gap between nanodosimetry and experimental microdosimetry. This work describes the first microdosimetric characterization at nanometric level of a 195.2 MeV/u carbon ion beam available at CNAO (National Centre for Oncological Hadron Therapy). The detector was properly placed at different depths in PMMA phantom across the depth-dose profile of the primary beam for measuring microdosimetric distributions for different simulated site sizes down to 25 nm at different depths.

The acquired spectra show that this TEPC is capable of reproducing the beam slowing down, showing a shift towards higher lineal energies as the primary particles slow-down. Moreover, the distributions at different simulated site sizes for the same depth are influenced by secondary electrons: smaller site size spectra exhibit a shift towards higher lineal energies as the site decreases, while this is not the case for more distal positions, where the edge of the spectra is almost independent of the simulated site size. Monte Carlo simulations performed with the FLUKA code show a good agreement with the experimental results obtained in the present paper.

Keywords: Microdosimetry; Nanodosimetry; Tissue Equivalent Proportional Counter (TEPC); Hadron therapy; CNAO; FLUKA.

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1. Introduction

Hadron therapy is a technique based on fast light ions - mainly protons and carbon ions - for treating radio-resistant tumors and those located close to organs at risk. In the last decades, use of hadron therapy has been spreading worldwide for cancer treatment because of its favorable depth-dose distribution as compared to conventional radiation therapy with high-energy photons and electrons. More specifically, the main advantages associated with the use of hadron beams as compared to photon or electron beams are *i)* a higher energy loss at the end of the penetration range (Bragg peak), *ii)* a high ballistic precision, allowing the possibility of treating cancers located near critical organs, *iii)* a higher relative biological effectiveness (RBE) at a definite absorbed dose. At present, there are 88 therapeutic centers treating patients with particle beams (Particle Therapy Co-operative Group, 2019). Most of them use fast proton beams, whereas 13 facilities (6 in Japan, 4 in Europe and 3 in China) employ carbon ion beams. Carbon ions offer, beside the favorable physical properties, also biological advantages over protons: higher RBE and lower oxygen enhancement ratio (OER), which refers to the biological sensitivity of tissue to the oxygen content in the tumor (Sørensen et al., 2011).

The assessment of the biological effective dose to characterize clinical hadron beams is based on absorbed dose, which is a macroscopic and averaged quantity not adequate to describe the energy deposition process at micrometric level, because it disregards the track structure (i.e. the spatial distribution of the interaction pattern) of ionizing charged particles in the target volume. Nowadays it is accepted that the initial features of radiation interactions within nanometric distances are strongly linked to the likelihood of biological damage at cellular level (Goodhead, 1994). Given the correlation between the biological effectiveness and the local energy deposition, an accurate knowledge of the physical properties and of the biological effects of therapeutic hadron beams at micrometric or nanometric level is important to perform accurate treatments.

A more precise physical description of energy deposition can be achieved through microdosimetry, which measures the statistical fluctuations of the local energy imparted at the micrometric level and track-nanodosimetry, devoted to the description of the pattern of particle interactions at the nanometric level. The tissue equivalent proportional counter (TEPC) is the reference radiation detector for measuring the microdosimetric properties of a particle beam, but the minimum site which can be measured by a standard TEPC operated in pulse mode is around 300 nm. Nanodosimeters, on the other hand, are capable of measuring

the single-event distribution of ionization cluster size for site dimensions from a few nanometers up to tens of nanometers, but only three detectors are available worldwide (Palmans et al., 2015).

For these reasons, it is interesting to lower the TEPC active volume down to smaller dimensions in order to measure the fluctuations of the energy absorbed in nanometric sites. In the past, a wall-less single-wire counter of 3.18 mm in diameter capable of measuring microdosimetric distributions down to 10 nm in simulated site size was developed (Kliauga, 1994). With this device, spectra of mono-energetic deuterons and oxygen ions in the range 500 - 10 nm were obtained. The counter resolution, however, was never measured, since the detector was not equipped with a calibration alpha source. A comparison between experimental data and Monte Carlo calculations highlighted that the size of the electron avalanche depends strongly on the position of the primary ionization, since the gas multiplication occurs throughout the whole sensitive volume (Olko et al., 1995).

A possible way to overcome this problem is to confine the electronic avalanche by exploiting a co-axial helix which forces the avalanche within a fixed volume around the anode wire. Consequently, an avalanche-confinement nano-microdosimetric TEPC capable of measuring microdosimetric spectra in the nanometric domain was designed and constructed (Bortot et al., 2017b). The response of this detector was characterized against fast neutron fields (quasi-monoenergetic and from a ^{241}Am-Be source) and 62 MeV/u helium ions, demonstrating its capability in performing microdosimetric measurements from 0.5 μm down to 25 nm in simulated site size (Bortot et al., 2018; Mazzucconi et al., 2019a).

This nano-microdosimetric TEPC was recently exploited for assessing the quality of the therapeutic CATANA (INFN-LNS) proton beam. The results showed that, for bigger sites, microdosimetric distributions followed the slowing down of the primary particles, while, for smaller sites, they exhibited a bimodal shape, in particular at smaller depths in PMMA. The comparison among different simulated volumes showed an increment of the dose-averaged lineal energy with the reduction of the site. A detailed description of all the results obtained in the framework of this characterization are described in a dedicated paper by Mazzucconi et al., 2019b.

A preliminary experimental characterization of the response of this detector to a 62 MeV/u carbon ion beam was performed in the past (Bortot et al., 2017b) and then compared with Monte Carlo simulations (Mazzucconi et al., 2018). Nevertheless, a deep and systematic study of the behavior and of the possible variations of the

microdosimetric distributions as a function of both the simulated site size (in the range 500 - 25 nm) and the depth across the whole carbon Bragg peak was never carried out.

This work aimed at performing the first nano-microdosimetric characterization of a therapeutic carbon ion beam available at CNAO (National Centre for Oncological Hadron Therapy), which exploited a 3D active scanning method. The avalanche-confinement TEPC was properly placed at six different depths in PMMA phantom across the depth-dose profile of the primary beam for measuring microdosimetric spectra from 0.5 µm down to 25 nm in simulated site size at each position. This systematic set-up allowed to study in details the variations of the shape of the distributions by moving towards a nanometric domain. The experimental results are compared with Monte Carlo simulations performed with the FLUKA code.

2. Materials and methods

2.1 The avalanche-confinement nano-microdosimetric TEPC

A TEPC is capable of measuring energy depositions in nanometric simulated sites as long as the electronic avalanche is confined in a defined region inside the sensitive volume of the counter in order to provide the requested energy resolution. A possible way to confine the electronic avalanche is to exploit a properly biased helix which forces the avalanche within a fixed volume around the anode wire, avoiding any significant multiplication taking place outside the helix itself.

By following this approach, an innovative cylindrical TEPC capable of performing microdosimetric measurements from 0.5 µm down to 25 nm in simulated site size, was designed and constructed. It is composed by three electrodes biased independently: a central anode wire (graphite, 1 mm in diameter), a cylindrical cathode shell (conductive plastic A-150 type, 13 mm in internal diameter and 1 mm in thickness) and a helix (gold-plated tungsten, 100 µm in diameter) made of 19 coils, 6 mm in diameter (Figure 1). This helix surrounds the anode wire and subdivides the sensitive volume into an external drift zone and an internal multiplication region. An orifice on the basis cap allows the gas flowing, while two aligned holes in the Rexolite caps contain a removable Cm-244 alpha source and a miniaturized solid state detector (SSD). This configuration allows to calibrate the TEPC by also varying the simulated site size and the polarization of the three electrodes. More details about the design of this TEPC can be found in Bortot et al., 2017a, 2017b.

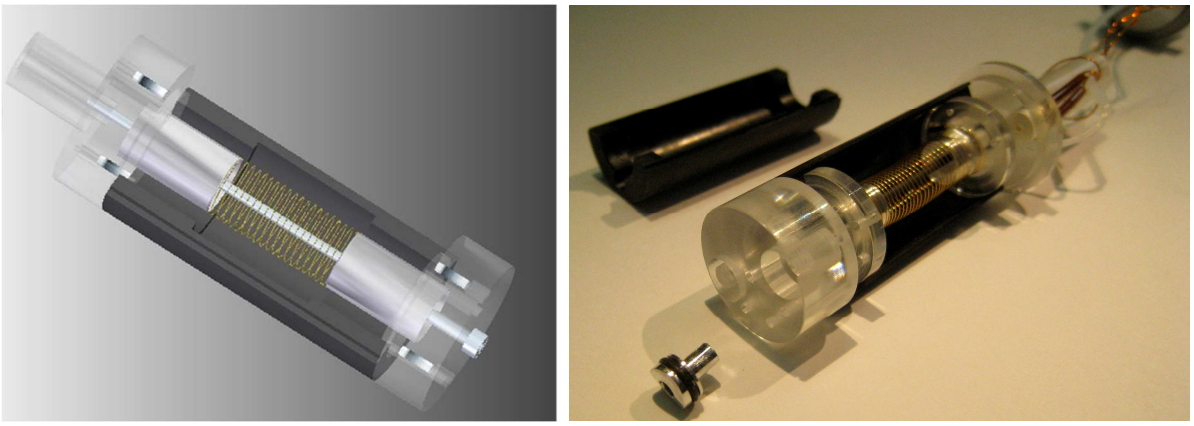

Figure 1: The avalanche-confinement TEPC (cylindrical sensitive volume 13 mm in diameter and length).

In order to simulate tissue sites in the nanometric domain, a very low gas pressure (down to about 1 mbar) has to be achieved and maintained constant during the whole irradiation time. For this reason, a customized and transportable vacuum and gas flow system was constructed to guarantee vacuum conditions and to ensure a continuous replacement of tissue equivalent gas inside the chamber, for preserving the high purity required for stable gas gain and for minimizing ageing and outgassing effects. (Bortot et al., 2014). Dimethyl ether (DME: $(CH_3)_2O$) is the selected filling gas for this avalanche-confinement TEPC: it can be considered as a tissue-equivalent gas, apart from the lack of nitrogen (ICRU Report 36, 1983).

2.2 Measurement campaign

The CNAO (National Centre for Oncological Hadron Therapy) is a clinical facility located in Pavia (Italy) conceived to supply hadron therapy treatments to patients by exploiting high-energy light ion beams such as protons and carbon ions using a 3D active scanning method. In particular, the CNAO clinical facility is equipped with a synchrotron capable of accelerating protons to kinetic energies in the range 60-250 MeV and carbon ions in the range 120-400 MeV/u. Energies of such beams cover a range in water up to about 38 cm, with a modulation step of 1 mm, complying with the requirements of clinical use (S. Rossi et al, 2011).

The beam quality of the CNAO carbon ion beam of 195.2 MeV/u, properly spread-out by using two thin PMMA ripple filters (2 mm in thickness each), was characterized at different simulated site sizes (in the range 500 - 25 nm) by placing the above described nano-microdosimetric TEPC downstream of a stack of several PMMA foils of different thickness for reproducing different depths across the Bragg peak. The experimental

set-up (in particular the carbon ion exit window, the PMMA stack and the TEPC) and the depth dose profile with the indication of the measurement positions are depicted in Figure 2.

Microdosimetric distributions for different nanometric sites (i.e. 500, 100, 50 and 25 nm) were acquired at each point of the depth dose profile. The raw data, in terms of pulse height spectra, have been calibrated against lineal energy by exploiting the calibration coefficients obtained by characterizing the TEPC response with the embedded Cm-244 alpha source (Bortot et al., 2017a). Since the detector shows an unconventional sensitive region (given by a hollow cylinder, i.e. the region between the helix and the cathode wall) and the carbon beam is strongly directional, the mean chord length is set equal to $0.612d$, where d is the dimension of the simulated site size (Mazzucconi et al., 2018). Finally, the frequency distributions were elaborated in the usual microdosimetric way for obtaining the dose probability density $d(y)$.

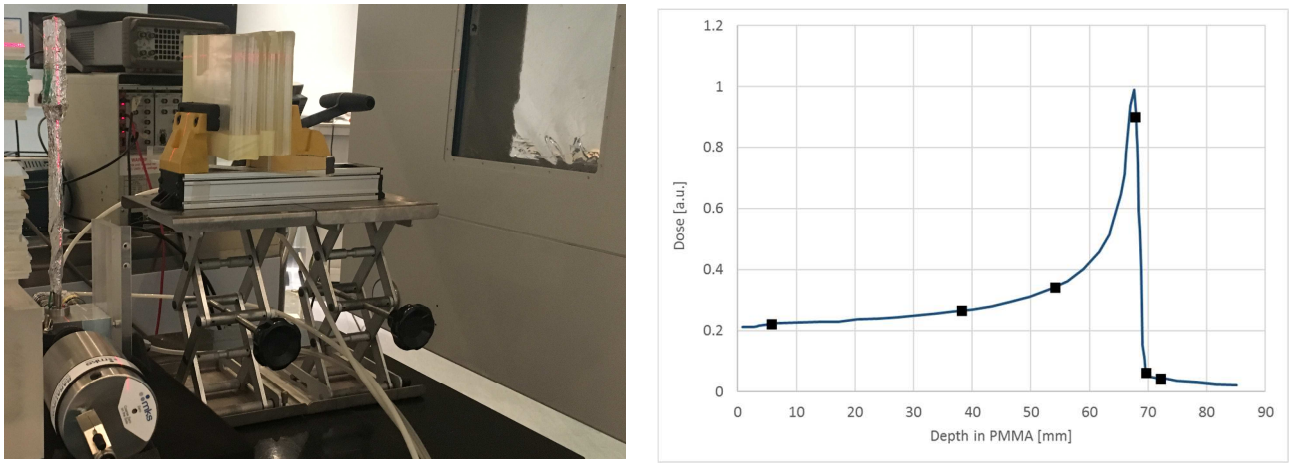

Fig. 2. Experimental set-up at CNAO (on the left): from left to right the TEPC, the PMMA stack and the carbon ion exit window are shown. Depth dose profile (blue solid line) of the 195.2 MeV/u carbon ion beam, in which the 6 measurement positions are depicted by black squares (on the right).

2.3 Monte Carlo simulations

A set of Monte Carlo simulations was performed with the FLUKA code (Ferrari et al., 2005; Böhlen et al., 2014). The geometry of the TEPC was reproduced strictly in FLUKA in order to simulate the response of the detector irradiated by the 195.2 MeV/u carbon ion beam.

The detector was then placed in the simulated carbon beam line including the two ripple filters described above and the PMMA foils for reproducing the different points across the dose distribution.

The electron production and transport thresholds were set to 1 keV in the sensitive region and in all the surrounding regions (e.g. cathode wall, anode, helix) and to 10 keV in the other detector regions that are not directly adjacent to the sensitive zone (e.g. aluminum case and surrounding air).

More details about the nano-microdosimetric simulations with this TEPC are discussed in detail in Mazzucconi et al., 2018.

3. Results and Discussion

3.1 Experimental microdosimetric distributions

The microdosimetric distributions measured at different depths across the carbon depth dose profile (5.76, 38.2, 54.2, 67.6, 69.7 and 72.2 mm) for different simulated site sizes (500, 100, 50 and 25 nm) are depicted in Figure 3. The lower is the simulated site size, the lower is the gas gain due to a lower amount of DME molecules, which causes a higher lineal energy threshold. For this reason, the microdosimetric distributions for the 25 nm site are partially cut. Moreover, the spectra which refer to the first two proximal positions (5.76 and 38.2 mm) are not plotted since they are below the acquisition threshold. Figure 3 shows that all the measured distributions shift towards higher lineal energies as the depth increases (from 5.76 mm to 69.7 mm), according to the beam slowing-down. In contrast, at 72.2 mm, which is beyond the Bragg peak, the microdosimetric spectra change dramatically due to the contribution of fragments, i.e. nuclei lighter than carbon generated by the projectile fragmentation during its trajectory inside the target. In particular, since the primary beam is completely stopped at this depth, the measured distributions are produced by fragments and their shape is widened over a larger lineal energy range, because of their wide energy range. It should be mentioned that the carbon fragments are always present throughout the depth dose distribution, but their contribution to the microdosimetric spectrum becomes evident only beyond the Bragg peak.

Figure 4 shows the comparison of different simulated site sizes at two depths (54.2 mm and 69.7 mm, proximal and distal, respectively). The most distal point plot (right side of Figure 4) shows that the carbon edge is almost independent of the simulated site size, while this is not the case for the proximal depth. The left side of Figure 4, in fact, highlights that the distributions, in particular in the higher lineal energy region, are modified strongly by the simulated site size. The site size reduction causes a shift of the right region of the distribution towards higher lineal energies, while the lower lineal energy region appears almost unchanged.

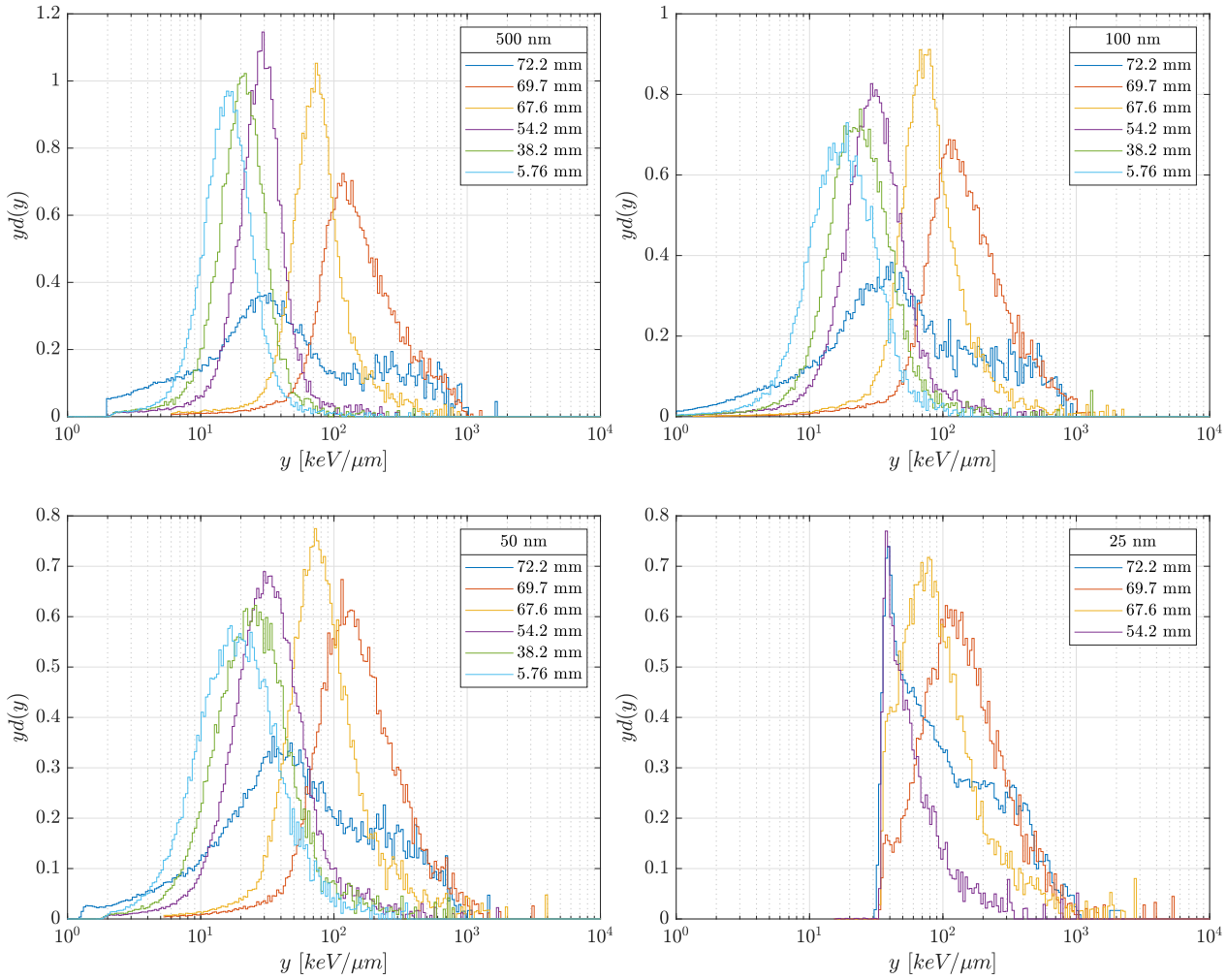

Fig. 3. Microdosimetric distributions measured at different depths across the carbon depth dose profile (5.76, 38.2, 54.2, 67.6, 69.7 and 72.2 mm) for different simulated site sizes (500, 100, 50 and 25 nm). For the 25 nm site, the first two proximal positions are not plotted since they were below the acquisition threshold.

This trend can be explained if the right side of the main peak is assumed to be produced by delta ray electrons behaving as stoppers, i.e. slow electrons injected into the sensitive volume by particles interacting in the surrounding regions and stopped before exiting the volume. In particular, it is likely that the trend described above is due to those electrons which cross most part of the volume before stopping.

In fact, for smaller simulated sites, stoppers have smaller energy, therefore higher lineal energy. It should be mentioned that all the particles which stop in the smallest volume would also stop in all the bigger sites, but in this last case the contribution of the same particles to the microdosimetric spectrum would affect a region at lower lineal energies, since the same imparted energy is divided by a higher mean chord length. A similar discussion was used for the calibration of TEPCs with the so-called electron edge (Conte et al., 2013).

It is worth to be mentioned that this dependence on the simulated site size was observed also irradiating the TEPC with a Cs-137 gamma ray source, a 62 MeV/u helium ion beam and the clinical proton beam of CATANA, as discussed in Bortot et al., 2017b and Mazzucconi et al., 2019a, 2019b, respectively. In spite of this, carbon ions produce microdosimetric spectra less affected by this behavior: the distribution is modified but does not show the peculiar bimodal shape observed with protons.

Kliauga (1994), analyzing the microdosimetric distributions of a high-LET oxygen ion beam, showed a low-LET peak produced by delta rays, whose position is depended on the simulated site size. In particular, the contribution of electrons for a 20 nm site is around 70 keV/µm, which is in agreement with the edge measured by this TEPC at 25 nm (Figure 4, on the left). It should be mentioned that the events measured in the region above 150 keV/µm could be ascribed to an increase of the variance of the distributions with the decrease of the simulated site size, maybe due to the gas multiplication.

However, this peculiarity will be investigated in more details in a future research in order to study the evolution of this shape for smaller nanometric sites (DNA like sites). In order to investigate this aspect, a new wall-less avalanche-confinement TEPC has been developed and installed inside the STARTRACK nanodosimeter (INFN-LNL) for comparing microdosimetric and nanodosimetric approaches for the same primary beam (Mazzucconi et al., submitted manuscript).

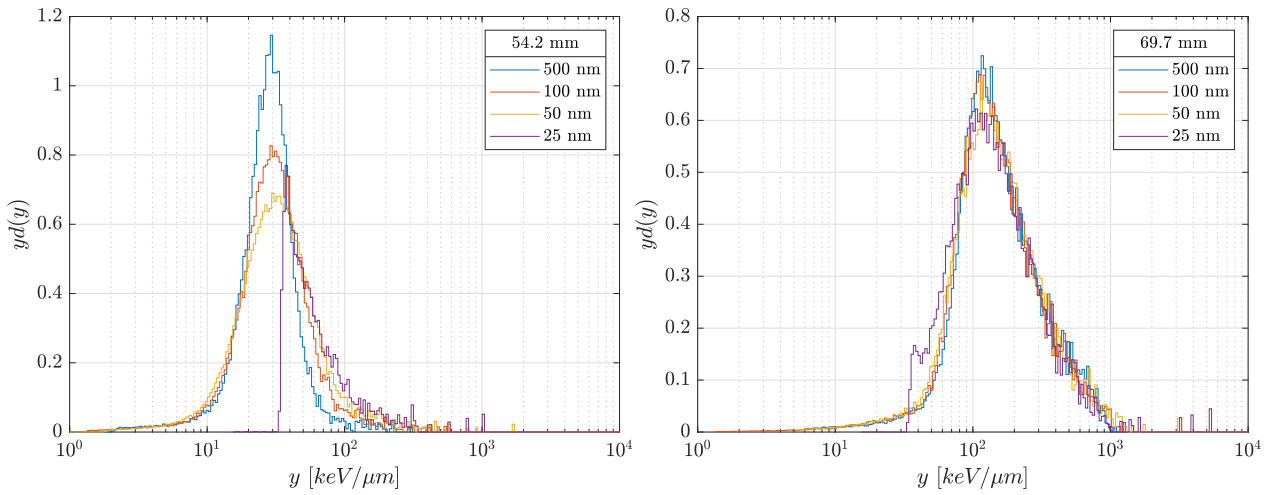

Fig. 4. Comparison between different simulated site size spectra (from 500 to 25 nm) for 54.2 mm (proximal depth) and 69.7 mm (distal depth).

3.2 Comparison between experimental and simulated microdosimetric spectra

The comparison between experimental data and FLUKA simulations for 100, 50 and 25 nm is shown in Figure 5. Previous works (Mazzucconi et al., 2018; Bortot et al., 2018) demonstrated that FLUKA is capable of reproducing microdosimetric distributions for carbon ions and neutrons down to 25 nm, in spite of the electron energy threshold that is set equal to 1 keV. Below this value the energy is assumed to be deposited locally. As expected, the experimental data are well reproduced by Monte Carlo simulations for all the investigated sites and, in particular, at 25 nm. At this size, the only discrepancy is due to the energy threshold: FLUKA is able to follow the whole distribution, while the experimental one is truncated below about 35 keV/µm.

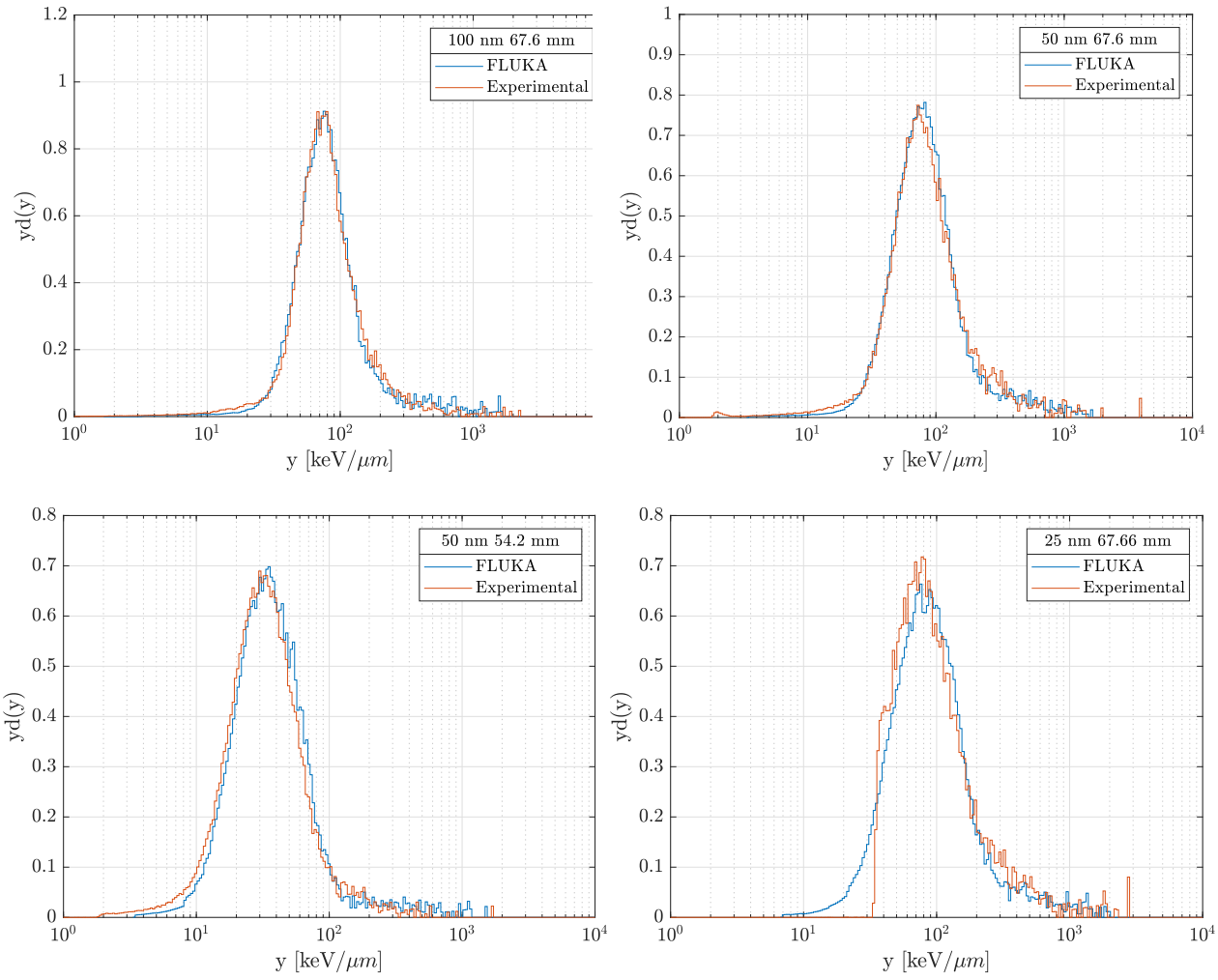

Fig. 5. Comparison between experimental data and FLUKA simulation for 100, 50 and 25 nm in simulated site size.

3.3 Dose-mean lineal energy

The dose-mean lineal energy ($\bar{y}_D$) values were calculated for all the distributions clearly above the threshold (i.e. 500, 100 and 50 nm) for all the considered depths across the Bragg peak (Figure 6). For all the sites, the trend follows the beam slowing-down that results in an increment of the stopping-power and, thus, of the $\bar{y}_D$. Nevertheless, as expected by the microdosimetric spectra (at 72.2 mm), the dose-mean lineal energies of the fragments drop to lower values. In particular, the $\bar{y}_D$ spans from about 25 keV/µm up to 200 keV/µm for the primary distributions and is reduced to 120 keV/µm beyond the Bragg peak.

In line with the microdosimetric spectra, a reduction of the site size results in an increase of the dose-mean lineal energy value. It should be mentioned that this increase could be also the consequence of the increase of the variance of the distributions, which, in turn, derives from the increase of energy loss straggling. This behavior was observed also for both protons and helium ions (Mazzucconi et al., 2019a, 2019b) and its origin has to be further investigated.

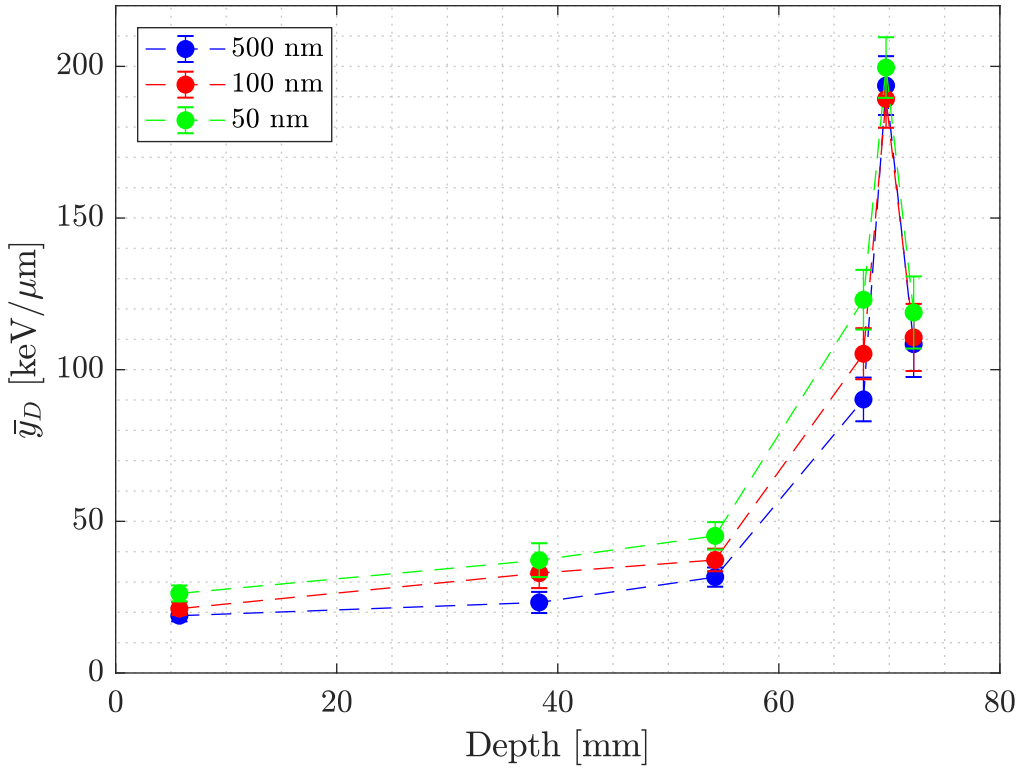

Fig. 6. Dose-mean lineal energies as a function of the depth across the carbon Bragg peak for 500, 100 and 50 nm in simulated site size. The uncertainty bars of the dose-mean lineal energies values are only statistical.

Conclusions

In this work, the avalanche-confinement TEPC developed by Bortot et al., 2017b, was exploited for the first time for performing a systematic microdosimetric description at nanometric level of the 195.2 MeV/u carbon ion beam available at CNAO. The detector was placed at different depths across the depth-dose profile of the primary carbon beam and different microdosimetric distributions for different simulated site sizes in the range 500 - 25 nm were acquired for each position.

The acquired spectra demonstrated that the TEPC was capable of reproducing the beam slowing down showing a shift towards higher lineal energy as the primary particles slowed-down. Different simulated site size distributions for the same depth turned out to be influenced by secondary delta ray electrons: small site size spectra exhibited a shift towards higher lineal energies as the site decreased, while this was not the case for more distal positions, where the edge of the spectra was almost independent of the simulated site size. This effect was reflected also in the dose-mean lineal energy values that depended on the simulated volume, especially for proximal positions.

Monte Carlo simulations performed with FLUKA showed a good agreement with experimental measurements down to 25 nm in simulated site size.

In the next future, a new wall-less avalanche-confinement TEPC installed inside the STARTRACK nanodosimeter (INFN-LNL) will allow to compare microdosimetric and nanodosimetric approaches for the same primary beam, by providing microdosimetric distributions at nanometer level against track-nanodosimetric distributions. This set-up will allow, for the first time, to study the feasibility of unfolding the nano-microdosimetric spectrum into a track-structure information, which is more related to the description of the radiation damage, with respect to the microdosimetric distribution.

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