Response of EBT3 radiochromic film dosimeters to proton and carbon ion hadrontherapy beams

Relatore
Prof. Paolo Russo

Candidata
Dott.ssa Roberta Castriconi
matr. N94/225

Anno Accademico 2014/2015
Response of EBT3 radiochromic film dosimeters to proton and carbon ion hadrontherapy beams

by

Roberta Castriconi (BSc. Physics)

This thesis work was carried out during March 2015 - March 2016 for fulfilling the requirements for the Diploma di Laurea Magistrale in Fisica (MSc. Physics) at University of Naples "Federico II", Naples, Italy.

The Istituto Nazionale di Fisica Nucleare (INFN) (Italy) approved scientifically and funded the research activities carried out in this work, within the research project RDH.

The following Institutions kindly provided access to their research or hospital facilities for the purposes of this work:

Istituto Nazionale di Fisica Nucleare, Sezione di Napoli, Naples, Italy

Fondazione CNAO, Centro Nazionale di Adroterapia Oncologica, Pavia, Italy

Ospedale San Raffaele, Milan, Italy

Heidelberg Ion-Beam Therapy Center (HIT), Heidelberg, Germany

Centro di Protonterapia, APSS, Trento, Italy
Response of EBT3 radiochromic film dosimeters to proton and carbon ion hadrontherapy beams

List of Contents

Preface.................................................................4

Introduction..............................................................................5

Chapter 1  Radiochromic EBT3 film dosimeters for radiotherapy and hadrontherapy........8
§ 1.1  Response of radiochromic films to proton and carbon ion beams.................13

Chapter 2  Materials and Methods.................................................18
§ 2.1  Film irradiation.................................................................18
§ 2.2  Film scanning.................................................................21
§ 2.3  Depth-dose measurement................................................25

Chapter 3  Dose-response curves................................................28
§ 3.1  Dose-response curves for photons and electrons - measurements at HSR...........29
§ 3.2  Dose-response curves for protons - measurements at CNAO, HIT and CPT........31
§ 3.3  Dose-response curves for carbon ions - measurements at CNAO and HIT........34

Chapter 4  Analysis of the EBT3 response to hadrons........................................36
§ 4.1  Response of EBT3 films to protons and carbon ions relative to photon..............36
§ 4.2  Depth-Dose curve in water for protons and carbon ions...............................43

Chapter 5  Correction methods for the under-response of EBT3 films for hadrontherapy....47
§ 5.1  Treatment Planning system correction procedure........................................47
§ 5.2  FLUKA simulation correction procedure..................................................50
§ 5.3  Proposal for a new correction procedure....................................................54

Conclusions....................................................................................58

References....................................................................................61

Acknowledgments.............................................................................63
Preface

When Roberta came to me one year ago, asking for a topic for her thesis out of the list of thesis available in my lab, she had only one theme in mind: among the topics I indicated, she chose to work on dosimetry for hadrontherapy. No hesitation was in her face when I replied that among all topics, that one was the most challenging and difficult to carry out for her (and for me), for its inherent complexity, and mainly for a number of problems related, I thought, to the difficult availability of suitable beamtime at proton and carbon ion therapy centers. I also pointed out that my experimental experience with hadron beams for radiation therapy was quite limited, but that if she wanted to go on that way, I would have stood by her, since she had selected not the easiest, but the hardest way. Her thesis will have then been on radiochromic film dosimetry for hadrontherapy.

The results of this thesis provide a very comprehensive characterization of the response of radiochromic dosimetric films (type EBT3) to high energy protons and carbon ions adopted in hadrontherapy centers, as well as to high energy photons and electrons routinely used for conventional radiotherapy.

I am proud of Roberta’s work. She worked really hard – as I promised her, and even more. It has been a unique privilege indeed, for me, to be on that way with her, an absolutely talented scientist. The merit of this respectable work is totally in her hands and mind, in the countless days and nights she dedicated to experiments, to literature readings, to discussions, to disputes with her thesis supervisor, to scientific writings and reports, interleaved with many coffees.

When the Emperor Frederick II von Hohenstaufen founded this University, on 5th June 1224, he was thinking of all those students thirsty for knowledge, the very best minds of his kingdom. It is the presence and the push of such brilliant, unique women and men that makes our noble work so joyful, and exciting: thank you, Roberta!

Paolo Russo
Università di Napoli Federico II
Napoli, 17th February, 2016.
**Introduction**

Intensity modulation applied in conventional photon radiotherapy (IMRT) is in daily clinical use in modern radiation oncology. Furthermore, hadrontherapy beams (presently available in specialized clinical facilities as proton and carbon ion beams) have attracted growing interest as an effective tool for cancer treatment in selected cancer pathologies and therapeutic strategies, because of their high dose localization and high cell-killing effect at the Bragg peak of the energy deposition curve. In both cases, complex radiation fields are applied to optimize the dose to the three-dimensional tumour volume, while at the same time minimizing side effects to surrounding healthy tissue. Therefore, a tool with high spatial resolution is required for the verification of 3D dose distribution measurements, featuring adequate dose precision and accuracy, reliability, ease of handling, low cost. For such purpose, dosimetric films are available which acquire a blue colour and darken in response to absorption of ionizing radiation; they are a form of radiochromic film dosimeters presently produced by one manufacture as GAFCHROMIC™ films (International Specialty Products, Wayne, NJ, USA).

Radiochromic films (e.g. EBT3 type) are adopted routinely for dosimetric verification and for quality assurance at linear accelerators used for conventional radiotherapy with photon and electron beams; however, their use in hadrontherapy is limited to beam verification and quality assurance procedures. Indeed, the use of such dosimeters in complex radiation beam geometries – which imply high dose gradients – requires the careful setup of a film analysis and calibration procedure, in which the nonlinear response of the film vs. dose is accurately determined and described by suitable fitting functions. While there are standard procedures for calibration of such radiochromic
films for photon radiotherapy beams, in case of hadron beams a peculiar phenomenon in the film response has to be considered. Indeed, in contrast to sparsely ionizing radiation, irradiation by ions leads to a strongly inhomogeneous dose deposition in matter and specifically in the sensitive layer of the film. A quenching effect occurs in the film response, consisting of an under-response of the EBT3 to ion beams with respect to MV-photon beams, at equal dose levels, likely due to the ion track structure. This under-response introduces a bias in the dose estimation and prevents from deriving the correct value of the absorbed dose from a previously determined calibration curve. Hence, the film response will be dependent, to some extent, on the local value of the ion stopping power in the film sensitive layer, at the position in the beam where the film is located along the energy deposition path in the irradiated material. A common way of assessing this peculiar dose response is via comparison of the response of the film to a conventional radiotherapy beam (e.g. as produced by clinical linear accelerators operated at 6 MV to 18 MV potential) at fixed dose values in a tissue-equivalent material (e.g. water, acrylic, solid water, etc.). The reference dose values are usually determined via ionization chamber dosimeters.

The aim of this work is investigate the response of EBT3 films to proton and carbon ion beams, and to compare it with photon and electron beams response, for assessment of a dose-response correction procedure. To this purpose, a series of measurement shifts have been granted at major hadrontherapy centers (in Pavia, Heidelberg, Trento) and at the Medical Physics Department of a large Hospital (Milan, Italy), within the activity of the RDH project of Istituto Nazionale di Fisica Nucleare (INFN).

The structure of this thesis follows this scheme.
Chapter 1 describes the phenomenon of the under-response of EBT3 radiochromic films with respect to their response to the same dose of high-energy X-ray photons.

Chapter 2 contains a description of the film irradiations at the various Hospital sites where the measurements were performed, as well as a description of the data elaboration methods.

Chapter 3 contains the analysis of the data of the dose-response curves for photons, electrons, protons and carbon ions.

Chapter 4 contains the results for the quantification of the quenching effect for the EBT3 film response to hadrons relative to photons and the measurement of the depth-dose in water both with protons and carbon ions.

Chapter 5 presents some literature studies in the investigation of a procedure for assessment of a dose-response correction procedure for hadrontherapy, as well as the sketch of a new correction procedure based on validated Monte Carlo simulations and EBT3 film measurements.
Chapter 1. *Radiochromic EBT3 film dosimeters for radiotherapy and hadrontherapy*

In cancer radiation therapy, an accurate dose determination and a precise dose delivery to the tumour are needed for a better treatment in terms of higher tumour control and lower post irradiation complications. At the state of the art, new dynamic dose delivery techniques such as intensity modulated radiotherapy or scanning proton and ion beams are being increasingly applied in radiotherapy. The aim of these techniques is to achieve the highest possible conformation of the delivered dose to the target volume and reduction of the dose to the surrounding normal tissue. Thus, precision treatment techniques, irregular fields and steep dose gradients are applied in order to achieve dose distribution that are highly conformal to the tumour. Under these conditions, a high spatial and dosimetric accuracy during the treatment delivery is of crucial importance for the effectiveness and the success of the prescription. Therefore, the patient plan verification before the dynamic dose delivery requires a method that makes it possible to measure the dose at many representative points at the same time. For this purpose, use of diode or ionization chamber arrays in regions of high dose gradients is limited due to too short (mm to cm) spacing of individual detector elements. Then, continuous 2D dosimetric media with high spatial resolution are especially suitable [8].

Film dosimetry was developed and optimized into a powerful tool for radiotherapy treatment verification and quality assurance. Film dosimeters present evident advantages for being 2D detectors that offer permanent records of the ionizing dose distribution measured with a high spatial resolution [4].
In particular, radiochromic films (GAFCHROMIC™, International Specialty Products, Wayne, NJ, USA – a business unit of Ashland [18]) produce the radiation-induced dose map by the self-developing post-irradiation process [4, 14].

Radiochromic films use a radiation-sensitive dye (usually diacetylene monomers organised into microcrystals and embedded in a gelatin binder) to measure the energy of ionizing radiations. Upon irradiation, a solid state polymerization (formation of polydiacetylene dye polymers) takes place and the film adopts a progressively darkening (figure 1.2-b). Further radiochromic film developments led to the EBT (External Beam Therapy) GAFCHROMIC™ film model, designed to replace silver halide radiographic film for the quality assurance procedures in radiotherapy. The EBT model retained all of the advantages of conventional silver halide film (2D dosimetry, thinness, permanent record, etc.) but without its numerous disadvantages like necessity of chemical development, sensitivity to visible light, strong energy dependence, etc. [3]. For clinical applications, the manufacturer improved the film response uniformity resulting in EBT2 film model and subsequently the latest EBT3 model (introduced in 2012) – which now replaces all previous models in the clinical practice.

The GAFCHROMIC™ EBT3 radiochromic dosimetry film is comprised of a single active layer, nominally 30-μm thick. The active layer is between two 125-μm thick transparent polyester substrates; the polyester substrate has a special surface treatment containing microscopic silica particles that minimize formation of Newton’s rings interference patterns in images acquired using flat-bed scanners (figure 1.1). The EBT3 film is nearly tissue equivalent and it can be immersed in water.
This model is suitable for a wide dose range (1 cGy to 40 Gy) in which it shows energy-independent dose response. The main absorption band in the absorption spectra for the EBT3 model is centered at 636 nm (figure 1.2).
Indeed, the high spatial resolution, energy independence of response and near tissue-equivalent of EBT3 film make it suitable for dose distribution measurements in radiation fields with high dose gradients [5].

As for other dosimeters, a radiochromic film dosimetry system provides an absolute dose as a result of measurement. However, one needs a calibration curve to convert the response of the film into absolute dose. For this purpose, the film is exposed to several known dose levels determined using a calibrated ionization chamber and the corresponding film darkening is measured usually with a flat-bad optical scanner. Since the calibration curve is determined for a given radiochromic film dosimetry system (film
model), for the specific densitometer used (usually a flat-bed scanner) and for the analysis protocol, such a system is considered to be a reference dosimetry system. Response of the radiochromic film to irradiation is commonly expressed in terms of the change in its optical density, which represents the difference in optical densities of the same piece sampled before and after irradiation. On the whole, the process of radiochromic film dosimetry can be divided into two distinct stages, as shown in figure 1.3: the first is the calibration procedure, during which film pieces are irradiated to known dose values; the second one is the measurement of the unknown dose to which the film is exposed, by measurement of the film optical response and use of the calibration curve obtained during the calibration.

The EBT3 films are widely used for dosimetry in conventional radiotherapy to verify whether the dose delivered to the patient coincides with the one calculated by the treatment planning system. In hadrontherapy dosimetry, the radiochromic films are scarcely used for such dose verification tasks because they show a significant under-response in dose [10, 12]. In contrast to sparsely ionizing beams, irradiations by ions lead to a strongly inhomogeneous dose deposition on a microscopic level and a quenching effect in the film response occurs. Indeed, their response depends on the kinetic energy of the ions and corresponding linear energy transfer (LET) of the radiation. This effect has significant consequences in the case of protons and carbon ions that lose energy mainly at the end of their path (Bragg peak) where the LET becomes higher – due to the low kinetic energy of the slowing-down ions – and the dosimeter response becomes lower [5]. Indeed, the darkening effect caused by the presence of organic monomers (which polymerize under irradiation and which allows to measure an increased optical absorption with increased absorbed dose) is compromised at high LET
Irradiations. The polymerization sites are spaced out with some separation: if all sites close to a single ionizing particle track are hit, the polymerization of the film is locally saturated and part of the energy loss remains unmeasured. In terms of LET this implies that the number of radiation-induced activated polymerization sites increases with LET until eventually no more sites are available for activation and the polymerization stops locally [17]. As a result, ionization chambers are utilized rather than radiochromic films, for the dosimetry quality controls routinely performed in hadrontherapy treatment planning. The radiochromic films are used only for quality assurance purpose, e.g. for beam verification and geometric accuracy determinations. In order to obtain precise results on the spatial distribution of the absorbed dose in tissue exposed to ion beams from dose images achieved with radiochromic films, suitable corrections of the acquired data are necessary. Research in this field started recently, in particular by Italian teams working at CNAO and at INFN-LNS [5,7].

1.1 – Response of radiochromic films to proton and carbon ion beams

For radiochromic EBT films the dose-response and the corresponding quenching were studied in proton and carbon ion medical beams – in the plateau region of the Bragg curve [13]. The quenching effect was analysed as a function of the ion type, energy and particle fluence. To quantify this effect, the measured values of the dose-response relation were used to calculate the relative efficiency, \( RE \), of the EBT film, where

\[
RE = \left. \frac{D_{\text{photon}}}{D_{\text{ion}}} \right|_{\text{netOD}}
\]  

(1.1)
Figure 1.4 Dose-response curves of (a) protons and (b) carbon ions for four different energies. The dose-response curve for $^{60}$Co photons is plotted for comparison (from ref. [13]).

Figure 1.5 The relative efficiency of EBT films for (a) protons and (b) carbon ions for the four different energies as a function of the photon dose (from ref. [13]).

This was defined, in accordance to the relative biological effectiveness, as the ratio of doses of photons $D_{\text{photon}}$ and ions $D_{\text{ion}}$ needed to produce the same film darkening $\text{netOD}$ as the one measured in the films irradiated by ions. In figure 1.4 the dose-response relationship for proton and carbon ions of different monoenergetic beams is shown in comparison to photons (dose-response for $^{60}$Co photons [11]). Figure 1.4-a shows that the proton curves coincide within uncertainties with the $^{60}$Co photon curve. All carbon ion curves, in figure 1.4-b, show under-response of the film over the whole dose range in comparison to $^{60}$Co photon beam. From the same study, in figure 1.5 the relative efficiency of EBT films is plotted as a function of the photon dose. For protons the relative response is compatible with unity and there are no significant differences for the various energies.
For carbon ions the relative efficiency amounts to about 0.7 – corresponding to a quenching of about 30% – while no dependence on the dose and thus on the fluence is observed.

Moreover, in the literature the response of the EBT films was studied in order to obtain the depth-dose curve for the depth-dose verification of active scanning proton beams [18]. The film response is strongly dependent on the proton energy at the Bragg peak, where the quenching effect may occur. Figure 1.6 (from ref. 15) shows the comparison of depth-dose curves measured by EBT films (films were exposed parallel to the beam axis in a solid water phantom) with those measured by the ionization chamber (parallel plate Markus chamber performed in a water tank) for several monoenergetic proton beams. The energy range was from 76 MeV to 186 MeV, which correspond to about 50 mm to 230 mm proton range in water. The measurements with the ion chamber were normalized at the maximum dose value;
The depth darkening distributions for carbon ion beams of 260 MeV/u at five different entrance dose values and (b) the depth-dose distributions measured by EBT films (for two different entrance dose values) and by ionization chamber (IC) – film data were normalized to match the chamber data at depth of 20 mm (from ref. [10]).

The data sets of EBT films were rescaled to the ion chamber dose measurements on the entrance plateau of the beam at a depth of 20 mm in water.

It can be seen that there is a good agreement between EBT films and ion chamber results, except for a lower peak-to-plateau ratio than that measured with the chamber. The depth-dose curves obtained with the EBT film show a 10 % to 20 % dose reduction at the Bragg peak region.

The response of the EBT films was also investigated in order to obtain the depth-dose curve for the depth-dose verification of active scanning carbon ion beams [10,12]. The EBT film was placed in a solid water phantom (slabs of tissue-equivalent material to water) parallel to the incoming beam and irradiated with a carbon ion beam of 260 MeV/u, which corresponds to about 130 mm range in water [10]. The depth darkening distribution for various dose regions is shown in figure 1.7-a. All peak positions are independent of the dose.
Moreover, figure 1.7-b shows the results of the depth-dose distributions measured by EBT films and by ionization chamber (performed in a water tank). The comparison of the data shows that the increase of the quenching effect is significant for the LET dependencies of the films toward the Bragg peak region. This is interpreted as a dependence of the response of the sensitive layer of the film on the energy-dependent LET of the particles, whose largest variation occurs at the distal end of the depth-dose curve across the Bragg peak. However, the peak positions are in good agreement with those measured by the chamber.
Chapter 2. *Materials and Methods*

The response of GAFCHROMIC™ EBT3 films (Lot #: 12011401) to proton and carbon ion beams was investigated and compared with photon and electron beams response, for assessment of a dose-response correction procedure. The dose-response relationship was evaluated in the same dose range 0.4 – 20 Gy for all radiation types.

2.1 – *Film irradiation*

The irradiations were performed at ‘National Center for Oncological Hadrontherapy’ (CNAO, Pavia, Italy – figure 2.1-a), at ‘Heidelberg Ion-Beam Therapy Center’ (HIT Heidelberg, Germany – figure 2.1-b) for proton and carbon ion beams; at ‘Proton Therapy Center’ (CPT Trento, Italy – figure 2.1-c) for proton beams and at ‘San Raffaele Hospital’ (HSR Milan, Italy) for photon and electron beams.

The energies analysed at CNAO for protons were 63, 150 and 230 MeV, corresponding to the Bragg peak position in water at 30, 151 and 320 mm, respectively. The energies for carbon ions were 115 MeV/u and 400 MeV/u, corresponding to the Bragg peak position in water at 30 mm and 270 mm, respectively.

The energies analysed at HIT were 150 MeV for protons and 250 MeV/u for carbon ions, corresponding to the Bragg peak position in water at 159 mm and 125 mm, respectively.

The energies analysed at CPT were 90 MeV and 180 MeV for protons, corresponding to the Bragg peak position in water at 63 mm and 216 mm, respectively.
Figure 2.1 (a) The main accelerator of CNAO is a synchrotron able to accelerate protons (extracted in the energy range of 60–250 MeV) and carbon ions (100–400 MeV/u). Outside the ring there are four extraction lines, leading the extracted beam into three treatment rooms. In each of the two side rooms, a horizontal beam is driven, while in the central hall both a horizontal and a vertical beam are directed. (b) The main accelerator of HIT is a synchrotron able to accelerate protons (50 – 220 MeV) and carbon ions (90 – 430 MeV/u). There are four extraction lines, leading the beam into three treatment rooms and into the experimental room (Q-A). In two treatment rooms and in the experimental one a horizontal beam is driven, while in the other treatment room the beam is directed by a gantry able to rotate over 180° (b). (c) The accelerator of CPT is a cyclotron producing an extracted proton beam of 230 MeV. Along the transfer line, a degrader provided the selection of the protons in the energy range 70 – 230 MeV. There are three extraction lines, two treatment rooms and an experimental room (Q-A). In the two treatment rooms, the beam is directed by a gantry able to rotate of 180°, while in the experimental one the beam is delivered horizontally.
For the irradiations with photon and electron beams the radiotherapy accelerator “Varian CLINAC 2100” was employed, operated at 6 MV and 18 MV for photons and at 6 MeV and 12 MeV for electrons. In addition, films were irradiated with a $^{60}$Co unit ("Leksell Gamma Knife Perfexion").

The EBT3 films were cut in 9 pieces, each of 4x4 cm$^2$ size, and each exposed to a different dose value, in order to obtain 9 dose points for all radiation type and energies. An example of exposed film pieces is shown in figure 2.2.

At the three hadrontherapy centers and for each proton and carbon ion beams irradiated at different energies, a homogeneous field of 6×6 cm$^2$ size was obtained for irradiating the film pieces using the beam-scanning mode. The particle fluence was increased for each field in order to obtain the nine desired dose values. For each irradiation the film piece was placed at the beam isocentre, perpendicular to the incident beam, behind 19 mm of water-equivalent solid RW3 slabs (corresponding to 20 mm water equivalent depth – conversion factor RW3 to water, 1.048). Additional RW3 slabs behind the film stabilized the setup.

Likewise, for photons and electrons a collimated field of 6×6 cm$^2$ size was obtained for irradiating each film piece, by increasing the accelerator monitor units for obtaining
increasing dose values. The piece for each irradiation was placed at the isocentre, perpendicular to the incident beam, behind acrylic (PMMA) slabs at a depth corresponding to the beam build-up position (respectively 15 mm for 6-MV photons, 35 mm for 18-MV photons, 13 mm for 6-MeV electrons and 27 mm for 12-MeV electrons water equivalent depth – conversion factor PMMA to water, 1.17). Additional PMMA slabs behind the film stabilized the setup.

For $^{60}$Co irradiation, the maximum field available was $16\times16$ mm$^2$, and each film was placed inside a water-equivalent solid phantom at the isocentre, then irradiated with a dose rate of 2.94 Gy/min.

### 2.2 – Film scanning

An Epson Perfection V750 Pro flat-bed scanner was used in transmission mode with 72 dpi scanning resolution (image sampling of 0.353 mm/pixel). The optical characteristic curve of the scanner is shown in figure 2.3. It was determined by scanning a transmittance grayscale step-wedge (KODAK step tablet No. 1 – 51450-731). The data point are well fitted by an exponential trend up to 3.05 in white-light optical density and down to 2000 in red-channel pixel value, while the minimum value of red-channel pixel value (corresponding to scanning a black opaque cardboard) is about 600.

Each film piece was placed in the landscape orientation in the middle of the flat-bed scanner and then scanned three times consecutively, both before and after irradiation, in order to account for scanner operation fluctuations. Five film pieces were taken as control films (zero-dose film pieces) to quantify the absorbance changes due to environment conditions. The control film represents a film piece that has not been irradiated but experienced the same story of the irradiated films.
The zero-light transmitted intensity value, which characterizes the background signal of the scanner, was determined with three scans of a black opaque cardboard.

The films were scanned in the 48-bit RGB mode and only the red channel, which provides the highest response, was analyzed. Indeed, in the red channel of the RGB image the increase of the pixel values at increasing dose values is higher than in the blue and green channels, due to the increased absorbance in the red one.
To minimize the impact of the film non-uniformity, for the same piece, the pixel values were sampled over 3 regions of interest (ROIs) (1x1 cm² size) in the same position as the before-irradiated image and as the after-irradiated image (figure 2.4). This operation was repeated for the three scans of each piece.

Likewise, to minimize the impact of the cardboard non-uniformity, the pixel values were sampled over ten ROIs (1x1 cm² size) in the area corresponding to the middle of the flat-bed scanner. This operation was repeated for the three scans of the black opaque cardboard. The average level of the background signal was then subtracted from the average level of the unexposed and exposed film pieces.

The optical density of the scanned film is defined as:

$$\text{OD} = \log_{10} \left( \frac{PV_{0}}{PV_{film}} \right)$$  \hspace{1cm} (2.1)

where $PV_{film}$ is the pixel value in a given position in the film and $PV_0$ is the maximum pixel value (corresponding to $2^{16}$ for a 16 bit digital image). In order to account for the intrinsic optical density of the film before exposure, one takes the difference of the optical densities of exposed and unexposed films [2]:

$$\text{OD} = \log_{10} \left( \frac{PV_0}{PV_{exp}} \right) - \log_{10} \left( \frac{PV_0}{PV_{unexp}} \right) = \log_{10} \left( \frac{PV_{unexp}}{PV_{exp}} \right)$$  \hspace{1cm} (2.2)

Then, by evaluation of the average value in a ROI and subtraction of the background, one obtains the expression for the optical density taking into account all the effects previously mentioned:

$$\text{OD} = \log_{10} \left( \frac{PV_{unexp} - PV_{bckg}}{PV_{exp} - PV_{bckg}} \right)$$  \hspace{1cm} (2.3)
where $\overline{PV}$ (respectively, $\overline{PV}_{\text{unexp}}$ for unexposed film, $\overline{PV}_{\text{exp}}$ for exposed film and $\overline{PV}_{\text{bckg}}$ for black cardboard) is the average pixel value determined as a weighted mean of pixel values over the ROIs, where the corresponding weights are the standard deviations of pixel values in each ROI. The uncertainty $\sigma_{OD}$ (standard error) of the darkening was determined through error-propagation analysis:

$$\sigma_{OD} = \frac{1}{\ln(10)} x \sqrt{\frac{\sigma_{PV_{\text{unexp}}}^2}{(\overline{PV}_{\text{unexp}} - \overline{PV}_{\text{bckg}})^2} + \frac{\sigma_{PV_{\text{exp}}}^2}{(\overline{PV}_{\text{exp}} - \overline{PV}_{\text{bckg}})^2} + \frac{(\overline{PV}_{\text{unexp}} - \overline{PV}_{\text{exp}})^2}{(\overline{PV}_{\text{exp}} - \overline{PV}_{\text{bckg}})^2} \sigma_{PV_{\text{bckg}}}^2} \quad (2.4)$$

In the equation (2.4) the assumption is made that the fluctuation in the pixel values of exposed and unexposed films can be summed in quadrature, i.e. that they are random and independent uncertainties.

The net optical density $\text{net}\text{OD}$ is commonly used to quantify the darkening of the film:

$$\text{net}\text{OD} = OD - OD_{\text{ctrl}} = \log_{10} \left( \frac{\overline{PV}_{\text{unexp}} - \overline{PV}_{\text{bckg}}}{\overline{PV}_{\text{exp}} - \overline{PV}_{\text{bckg}}} \right) - \log_{10} \left( \frac{\overline{PV}_{\text{ctrl}} - \overline{PV}_{\text{bckg}}}{\overline{PV}_{\text{exp}} - \overline{PV}_{\text{bckg}}} \right) \quad (2.5)$$

where $OD_{\text{ctrl}}$ is the optical density of the control film. The corresponding uncertainty is given by

$$\sigma_{\text{netOD}} = \sqrt{\sigma_{OD}^2 + \sigma_{OD_{\text{ctrl}}}^2} \quad (2.6)$$

where $\sigma_{OD_{\text{ctrl}}}$ is the uncertainty of the optical density of the control film.
Here, as a result of the error analysis shown in the following section, the darkening of the EBT3 film has been expressed also by considering (as "film response" variable) the pixel value, $PV$, instead of the pixel OD:

$$PV = \left(\frac{PV_{\text{unexp}} - PV_{\text{bkg}}}{PV_{\text{exp}} - PV_{\text{bkg}}}\right)$$

with the corresponding uncertainty

$$\sigma_{PV} = \sqrt{\frac{\sigma^2_{PV_{\text{unexp}}}}{(PV_{\text{exp}} - PV_{\text{bkg}})} + \frac{\sigma^2_{PV_{\text{exp}}}}{(PV_{\text{exp}} - PV_{\text{bkg}})} + \frac{(PV_{\text{unexp}} - PV_{\text{exp}})^2}{(PV_{\text{exp}} - PV_{\text{bkg}})^2} \sigma^2_{PV_{\text{bkg}}}}$$

In order to take into account the contribution of the control film, the net pixel value, $\text{netPV}$, with the corresponding uncertainty, $\sigma_{\text{netPV}}$, were used:

$$\text{netPV} = PV - PV_{\text{ctrl}} = \left(\frac{PV_{\text{unexp}} - PV_{\text{bkg}}}{PV_{\text{exp}} - PV_{\text{bkg}}}\right) - \left(\frac{PV_{\text{ctrl}}_{\text{unexp}} - PV_{\text{bkg}}}{PV_{\text{ctrl}}_{\text{exp}} - PV_{\text{bkg}}}\right)$$

$$\sigma_{\text{netPV}} = \sqrt{\sigma^2_{PV} + \sigma^2_{PV_{\text{ctrl}}}}$$

The radiochromic film dose-response was expressed as dose as a function of the measured darkening. Consequently, the data can be fitted to a curve used to convert measured darkening to unknown dose value.

### 2.3 – Depth-dose measurement

Irradiations with proton and carbon ion beams were performed at ‘National Center for Oncological Hadrontherapy’ (CNAO Pavia, Italy) for measuring the depth-dose curve in water for both ion types with EBT3 film. The beam energy for protons was 150 MeV, corresponding to the Bragg peak position in water at 151 mm. The beam energy for
carbon ions was 400 MeV/u, corresponding to the Bragg peak position in water at 270 mm.

For both proton and carbon ion beams, a homogeneous field of 3×3 cm² size was obtained for irradiating the film using the beam-scanning mode.

For a quantitative comparison of the EBT3 film response, a measurement of the depth-dose curve – under the same beam delivery conditions – was performed with a parallel plate ionization chamber (figure 2.5-a) of 0.02 cm³ sensitive volume (Markus Chamber, PTW model 34045) operated in a 30 x 30 x 30 cm³ water phantom (PTW model 41023). The water phantom consists of a tank with four walls and a base plate of 10 mm acrylic (PMMA) filled with water (figure 2.5-b). One wall has an entrance window (15 cm x 15 cm) of 3.05 mm thickness (corresponding to 3.5 mm of water). The phantom contains a precision holding device for precise positioning of the chamber (figure 2.5-c). The holder position can be varied along the longitudinal direction using an adjustable spindle drive (0.1 mm step). The measuring depth can be varied between 20 mm and 264 mm. In order to realize the measurement of the Bragg peak position at 270 mm in water, extra 4.8-cm thick RW3 slabs (corresponding to 5 cm of water) were added in front of the entrance window of the water phantom.

The EBT3 films were cut in pieces, each of 8×4 cm² size, and each was exposed at different position (along the Bragg curve of the corresponding ion) in the water tank; the EBT3 pieces were placed perpendicular to the incident beam. In order to place the EBT3 films correctly in the water tank, an adaptor was realized (in the mechanic’s workshop of INFN Napoli) consist of a PMMA frame, whose depth position could be varied using the spindle drive of the water phantom (figure 2.6).
After the irradiation, the EBT3 pieces were analysed as described in paragraph 2.2; for each film, the net optical densities were converted into dose values using the calibration curve realized respectively for 150 MeV protons and 400 MeV/u carbon ions. This was repeated for all pieces irradiated at the different position along the Bragg curve in water.
In order to assess the film response for each beam quality, the dose delivered ($D$), expressed as dose to water, was plotted as a function of the response ($\text{netPV}$ or $\text{netOD}$) of the corresponding film piece.

For the calibration curve, four possible fitting functions were investigated for all radiation data type:

\[
D = a \cdot \text{netPV}^2 + b \cdot \text{netPV} \quad (3.1)
\]

\[
D = a \cdot \frac{\text{netPV}}{1 + b \cdot \text{netPV}} \quad (3.2)
\]

\[
D = a \cdot \text{netOD} + b \cdot \text{netOD}^3 \quad (3.3)
\]

\[
D = a \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}} \quad (3.4)
\]

In order to evaluate the best fitting function, the reduced chi-square $\chi^2$ values of the fit were determined and compared. The fitting functions were evaluated with the commercial software Origin 8 Pro data analysis and graphic package (OriginLab Corporation, Northampton, MA, USA). The expression of each fitting function was used to recalculate the dose values and the corresponding error (as a result of the experimental uncertainty and fitting error); then the relative errors were compared. The following formulae represent the relative standard error, $\sigma_D(\%)$, expressed in percent, obtained through the error-propagation of the corresponding fitting function divided by the corresponding recalculated dose value $D_{\text{fit}}$. In propagating the error, the experimental uncertainty ($\sigma_{\text{netPV}}$ or $\sigma_{\text{netOD}}$) and the fitting parameter error ($\sigma_a$ and $\sigma_b$) were taken into account.
\[
\sigma_D(\%) = \frac{\sqrt{\text{netPV}^2 \cdot \sigma_a^2 + \text{netPV}^4 \cdot \sigma_b^2 + (a + 2 \text{netPV} \cdot b)^2 \cdot \sigma_{\text{netPV}^2}}}{D_{\text{fit}}} \times 100
\]  
(3.5)

\[
\sigma_D(\%) = \frac{\sqrt{\text{netPV}^2 \cdot \sigma_a^2 + \left(\frac{a \cdot \text{netPV}^2}{1 + b \cdot \text{netPV}^2}\right)^2 \cdot \sigma_b^2 + \left(\frac{a}{1 + b \cdot \text{netPV}^2}\right)^2 \cdot \sigma_{\text{netPV}^2}}}{D_{\text{fit}}} \times 100
\]  
(3.6)

\[
\sigma_D(\%) = \frac{\sqrt{\left(\text{netOD}^2 \cdot e^{b \cdot \text{netOD}}\right)^2 \cdot \sigma_a^2 + (a \cdot \text{netOD}^2 \cdot e^{b \cdot \text{netOD}})^2 \cdot \sigma_b^2}}{D_{\text{fit}}} \times \frac{\sqrt{(a \cdot e^{b \cdot \text{netOD}} + a \cdot b \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}})^2 \cdot \sigma_{\text{netOD}^2}}}{D_{\text{fit}}} \times 100
\]  
(3.7)

\[
\sigma_D(\%) = \frac{\sqrt{(\text{netOD}^2 \cdot e^{b \cdot \text{netOD}})^2 \cdot \sigma_a^2 + (a \cdot \text{netOD}^2 \cdot e^{b \cdot \text{netOD}})^2 \cdot \sigma_b^2}}{D_{\text{fit}}} \times \frac{\sqrt{(a \cdot e^{b \cdot \text{netOD}} + a \cdot b \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}})^2 \cdot \sigma_{\text{netOD}^2}}}{D_{\text{fit}}} \times 100
\]  
(3.8)

### 3.1 – Dose response curves for photons and electrons – measurements at HSR

In this section the dose-response curves and the result of the data analysis are shown for the photon and electron beams during the measurement sessions at ‘San Raffaele Hospital’ (HSR Milan, Italy).

Figure 3.1 shows the measured dose-response curves for different energies of photon and electron beams in terms of \(\text{netPV}\) (a) and \(\text{netOD}\) (b), respectively. Table 3.1 shows the results of the analysis of the fitting functions for photon and electron beams in terms of reduced chi-square \(\tilde{\chi}^2\). Table 3.2 shows the total relative error (minimum and maximum values) of the dose values when the dose was calculated from each fitting function. For the choice of the best fitting function, the selection criterion will be based on the analysis of the reduce chi-square \(\tilde{\chi}^2\) and on the total relative error \(\sigma_D(\%)\).
**Figure 3.1** Dose-response curves for different energies of photon and electron beams in terms of (a) netPV and (b) netOD. The data points are connected with a line segment for eye guidance.

**Table 3.1** Results of the analysis of the fitting functions for photon and electron beams in terms of reduced chi-square $\tilde{\chi}^2$.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Photons $\tilde{\chi}^2$</th>
<th>Electrons $\tilde{\chi}^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D = a \cdot \text{netPV} + b \cdot \text{netPV}^2$</td>
<td>1.31 1.26 2.40</td>
<td>0.86 7.65</td>
</tr>
<tr>
<td>$D = \frac{a \cdot \text{netPV}}{1 + b \cdot \text{netPV}}$</td>
<td>1.50 0.29 1.17</td>
<td>0.16 7.03</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} + b \cdot \text{netOD}^3$</td>
<td>9.24 3.31 4.32</td>
<td>5.82 11.2</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}}$</td>
<td>5.17 9.46 9.82</td>
<td>7.15 13.5</td>
</tr>
</tbody>
</table>
Table 3.2 Total relative error (minimum and maximum value) of the dose values when the dose was calculated from each fitting function.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Photons $\sigma_d$ (%)</th>
<th>Electrons $\sigma_d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 MV</td>
<td>18 MV</td>
</tr>
<tr>
<td>$D = a \cdot \text{netPV} + b \cdot \text{netPV}^2$</td>
<td>0.8 – 1.5</td>
<td>0.8 – 1.7</td>
</tr>
<tr>
<td>$D = \frac{a \cdot \text{netPV}}{1 + b \cdot \text{netPV}}$</td>
<td>2 – 18</td>
<td>1.5 – 20</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} + b \cdot \text{netOD}^3$</td>
<td>1.4 – 2.2</td>
<td>0.9 – 1.8</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}}$</td>
<td>8.5 – 11</td>
<td>10 – 14</td>
</tr>
</tbody>
</table>

Specifically, from table 3.1 one can see that, the quadratic (3.1) and the linear (3.2) functions provide the lower $\hat{\chi}^2$ with respect to the cubic (3.3) and exponential (3.4) expressed in terms of netOD. Based on this initial selection, one proceeds to consider the total relative errors shown in table 3.2. Here, the relative error obtained using the quadratic function (3.1) is lower than for the linear one (3.2). Then, one can conclude that for all radiation types, the quadratic-like function (3.1) in terms of netPV provided the best agreement between the goodness-of-fit (in terms reduced chi-square $\hat{\chi}^2$) and fit precision (in terms of $\sigma_d$ (%) when the dose was calculated from fitting curve). The relative error $\sigma_d$ (%) for the quadratic-like function was less than 3% for all radiation type and energies data.

3.2 – Dose response curves for protons – measurements at CNAO, HIT and CPT

In this section the dose-response curves and the result of the data analysis are shown for proton beams measured during several shifts at ‘National Center for Oncological Hadrontherapy’ (CNAO Pavia, Italy), at ‘Heidelberg Ion-Beam Therapy
Center’ (HIT Heidelberg, Germany) and at ‘Proton Therapy Center’ (CPT Trento, Italy).

Figure 3.2 shows the measured dose-response curves for different energies of proton beams in terms of $netPV$ (a) and $netOD$ (b) respectively. Table 3.3 shows the results of the analysis of the fitting functions for proton beams in terms of reduced chi-square $\tilde{\chi}^2$.

Table 3.4 shows the total relative error (minimum and maximum value) of the dose values when the dose was calculated from each fitting function. For the selection of the best fitting function, following the analysis reported in paragraph 3.1, one obtained that the linear (3.2) and the cubic (3.3) functions provided the lower value of the reduced chi-square $\tilde{\chi}^2$ (table 3.3). However, as evident in table 3.4, the relative error obtained using the cubic function (3.3) is lower than for the linear one (3.2). To summarize, for all energies, the cubic-like function (3.3) in terms of $netOD$ was considered to provide the best agreement between the goodness-of-fit (in terms of reduced chi-square $\tilde{\chi}^2$) and fit precision (in terms of $\sigma_D$ (%) when the dose was calculated from fitting curve). The relative error $\sigma_D$ (%) for the cubic-like function was less than 3% for all energies.

**Table 3.3** Analysis of the fitting functions for proton beams in terms of reduced chi-square $\tilde{\chi}^2$.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Protons (CNAO) $\tilde{\chi}^2$</th>
<th>Protons (HIT) $\tilde{\chi}^2$</th>
<th>Protons (CPT) $\tilde{\chi}^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D = a \cdot netPV + b \cdot netPV^2$</td>
<td>31.2 8.25 8.67</td>
<td>20.3</td>
<td>8.41 17.1</td>
</tr>
<tr>
<td>$D = \frac{a \cdot netPV}{1 + b \cdot netPV}$</td>
<td>28.7 6.13 6.78</td>
<td>15.6</td>
<td>6.18 14.3</td>
</tr>
<tr>
<td>$D = a \cdot netOD + b \cdot netOD^3$</td>
<td>35.3 6.62 6.32</td>
<td>9.01</td>
<td>9.05 7.14</td>
</tr>
<tr>
<td>$D = a \cdot netOD \cdot e^{b \cdot netOD}$</td>
<td>94.2 19.2 19.8</td>
<td>38.9</td>
<td>30.7 36.2</td>
</tr>
</tbody>
</table>
Figure 3.2 Dose-response curves for different energies of proton beams in terms of (a) netPV and (b) netOD, respectively. The data points are connected with a line segment for eye guidance.

Table 3.4 Total relative error (minimum and maximum value) of the dose values when the dose was calculated from each fitting functions.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Protons (CNAO) $\sigma_d$ (%)</th>
<th>Protons (HIT) $\sigma_d$ (%)</th>
<th>Protons (CTP) $\sigma_d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63 MeV</td>
<td>150 MeV</td>
<td>230 MeV</td>
</tr>
<tr>
<td>$D = a \cdot \text{netPV} + b \cdot \text{netPV}^2$</td>
<td>3 – 5</td>
<td>1.6 – 2.9</td>
<td>1.6 – 2.8</td>
</tr>
<tr>
<td>$D = \frac{a \cdot \text{netPV}}{1 + b \cdot \text{netPV}}$</td>
<td>4 – 19</td>
<td>2.6 – 20</td>
<td>2.7 – 20</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} + b \cdot \text{netOD}^3$</td>
<td>2 – 3.3</td>
<td>1.3 – 2</td>
<td>1.2 – 2</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}}$</td>
<td>19 – 26</td>
<td>13 – 19</td>
<td>13 – 18</td>
</tr>
</tbody>
</table>
3.3 – Dose response curves for carbon ions – measurements at CNAO and HIT

In this section the dose-response curves and the result of the data analysis are shown for carbon ions beams measured during the shifts at CNAO and at HIT. Figure 3.3 shows the measured dose-response curves for different energies of carbon ion beams in terms of \( netPV \) (a) and \( netOD \) (b), respectively. Table 3.5 shows the results of the analysis of the fitting functions for carbon ion beams in terms of reduced chi-square \( \tilde{\chi}^2 \). Table 3.6 shows the total relative error (minimum and maximum value) of the dose values calculated with each fitting function. For the selection of the best fitting function, following the analysis reported in paragraph 3.1, the linear (3.2) and the cubic (3.3) functions provided the lower value of \( \tilde{\chi}^2 \) (table 3.5), but the relative error obtained using the cubic function (3.3) is lower than for the linear one (3.2) (table 3.6). In conclusion, for all energies, the cubic-like function (3.3) in terms of \( netOD \) provided the best agreement between the goodness-of-fit (in terms of reduced chi-square \( \tilde{\chi}^2 \)) and fit precision (in terms of \( \sigma_D(\%) \)).

![Table 3.5 Results of the analysis of the fitting functions for proton beams in terms of reduced chi-square \( \tilde{\chi}^2 \).](image)

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Carbon ions (CNAO) ( \tilde{\chi}^2 )</th>
<th>Carbon ions (HIT) ( \tilde{\chi}^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D = a \cdot netPV + b \cdot netPV^2 )</td>
<td>7.37</td>
<td>6.12</td>
</tr>
<tr>
<td>( D = \frac{a \cdot netPV}{1 + b \cdot netPV} )</td>
<td>7.19</td>
<td>4.96</td>
</tr>
<tr>
<td>( D = a \cdot netOD + b \cdot netOD^3 )</td>
<td>11.5</td>
<td>4.67</td>
</tr>
<tr>
<td>( D = a \cdot netOD \cdot e^{b \cdot netOD} )</td>
<td>10.8</td>
<td>13.6</td>
</tr>
</tbody>
</table>
Figure 3.3 Dose-response curves for different energies of carbon ion beams in terms of (a) netPV and (b) netOD respectively.

Table 3.6 Total relative error (minimum and maximum value) of the dose values when the dose was calculated from each fitting functions.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Carbon ions (CNAO) $\sigma_D$ (%)</th>
<th>Carbon ions (HIT) $\sigma_D$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D = a \cdot \text{netPV} + b \cdot \text{netPV}^2$</td>
<td>1.4 – 2.7</td>
<td>1.5 – 2.7</td>
</tr>
<tr>
<td>$D = \frac{a \cdot \text{netPV}}{1 + b \cdot \text{netPV}}$</td>
<td>2.7 – 21</td>
<td>2.6 – 22</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} + b \cdot \text{netOD}^3$</td>
<td>1.5 – 2.5</td>
<td>1.1 – 2</td>
</tr>
<tr>
<td>$D = a \cdot \text{netOD} \cdot e^{b \cdot \text{netOD}}$</td>
<td>9.5 – 14</td>
<td>11 – 17</td>
</tr>
</tbody>
</table>
Chapter 4.  *Analysis of the EBT3 response to hadrons*

As described in chapter 1, for hadron beams, the radiochromic films show an under-response dependent on the kinetic energy of the ions and corresponding linear energy transfer (LET) of the radiation. This has significant consequences – in particular for the case of protons and carbon ions analysed in this study – at the end of the ion path (Bragg peak) where the LET increases due to the decreasing residual kinetic energy of the ions. For this purpose, after the characterization of the response of the EBT3 films as a function of the applied dose in monoenergetic photon, electron, proton and carbon ion beams (discussed in chapter 3), in this section an analysis of the quenching effect is presented.

First, a quantitative comparison is carried out between the EBT3 film response to the hadron beams (in the plateau region of the Bragg-curve) and to conventional radiotherapy beams at fixed dose values.

Then, for evidencing the quenching effect – also along the path of the ions in matter (Bragg-curve) – a measurement of the Depth-Dose distribution in water is shown, carried out with the EBT3 films and with an ionization chamber.

4.1 – *Response of EBT3 films to protons and carbon ions relative to photons*

For EBT3 films the dose-response and the corresponding under-response were studied in proton and carbon ion medical beams for different monoenergetic beams. As described in chapter 2, the irradiation were performed in the plateau region of the Bragg-curve with the EBT3 films in a solid water phantom.
In order to compare the response of EBT3 films to proton and carbon ion beams with that to photon and electron beams (following [12] and [13]), the measured values of the dose-response relation were used to calculate the relative efficiency, $RE$ (eq. 1.1). Since for the energies and the dose values investigated here the dose-response for photons was the same as that for electrons – as discussed in chapter 3 and shown in figure 3.1 – in the following only the comparison between ions and 6-MV photon responses will be considered. Therefore, the relative dose-response (relative efficiency $RE$) was defined as the ratio of doses of photons $D_{\text{photon}}$ and ions $D_{\text{ion}}$ needed to produce the same film darkening netOD as the one obtained for ion beams.

$$RE = \frac{D_{\text{photon}}}{D_{\text{ion}}}_{\text{netOD}} \quad (4.1)$$

Then, using the netOD obtained for the films irradiated by ions, the dose values for photons were extracted from the corresponding calibration fitting curve.

Figure 4.1-a shows the dose-response for protons and for 6 MV photons. Then, figure 4.1-b shows the corresponding relative dose-response curves as a function of the photon dose, extracted from the calibration curve using the netOD obtained in the films irradiated by ions. In table 4.1, the relative dose-response $RE$ with uncertainty for protons are reported (referring to the data plotted in figure 4.1-b), showing that the uncertainty of the relative-response $\sigma_{RE}$ for all energies is of the order of 2%. Table 4.2 shows the fitting parameters obtained from the fitting function (when all data points in figure 4.1-b at the different energies are pooled) and the parameters obtained from the single fitting functions for the relative protons dose-response data for 63, 150 and 230 MeV at CNAO; 150 MeV at HIT; 90 MeV and 180 MeV at CPT.
As shown in figure 4.1-a, the curves measured for protons at all energies are practically coincident with that for irradiation with photons. Indeed, the relative dose-response data for protons in figure 4.1-b show an almost constant trend: a weighted linear fit to all data points pooled together gives a slope consistent with zero and an intercept of 0.984 ± 0.004 (table 4.2), where the error represents the fitting uncertainty.
Table 4.1 The relative dose-response ($RE$) with uncertainty, for protons.

<table>
<thead>
<tr>
<th>Energy (MeV)</th>
<th>63 MeV CNAO</th>
<th>150 MeV CNAO</th>
<th>230 MeV CNAO</th>
<th>150 MeV HIT</th>
<th>90 MeV CTP</th>
<th>180 MeV CTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNAO</td>
<td>0.97 ± 0.02</td>
<td>0.98 ± 0.02</td>
<td>0.96 ± 0.018</td>
<td>0.97 ± 0.018</td>
<td>0.97 ± 0.017</td>
<td>0.98 ± 0.018</td>
</tr>
<tr>
<td>CNAO</td>
<td>0.97 ± 0.018</td>
<td>0.97 ± 0.02</td>
<td>0.97 ± 0.017</td>
<td>0.97 ± 0.017</td>
<td>0.97 ± 0.017</td>
<td>0.97 ± 0.017</td>
</tr>
<tr>
<td>CNAO</td>
<td>0.97 ± 0.018</td>
<td>1.014 ± 0.019</td>
<td>1.011 ± 0.02</td>
<td>0.98 ± 0.019</td>
<td>0.98 ± 0.019</td>
<td>0.96 ± 0.018</td>
</tr>
<tr>
<td>CNAO</td>
<td>1.002 ± 0.019</td>
<td>0.99 ± 0.017</td>
<td>0.97 ± 0.017</td>
<td>1.02 ± 0.02</td>
<td>1.008 ± 0.019</td>
<td>1.003 ± 0.019</td>
</tr>
<tr>
<td>CNAO</td>
<td>0.97 ± 0.02</td>
<td>1.014 ± 0.02</td>
<td>1.006 ± 0.02</td>
<td>1.013 ± 0.02</td>
<td>1.02 ± 0.02</td>
<td>1.02 ± 0.02</td>
</tr>
<tr>
<td>CNAO</td>
<td>0.97 ± 0.02</td>
<td>0.97 ± 0.02</td>
<td>0.97 ± 0.02</td>
<td>0.96 ± 0.02</td>
<td>0.99 ± 0.02</td>
<td>0.99 ± 0.02</td>
</tr>
<tr>
<td>CNAO</td>
<td>0.96 ± 0.02</td>
<td>0.96 ± 0.02</td>
<td>0.97 ± 0.02</td>
<td>0.96 ± 0.02</td>
<td>0.99 ± 0.02</td>
<td>0.97 ± 0.02</td>
</tr>
</tbody>
</table>

This indicates that the response of EBT3 films to proton beams in the range 63 – 230 MeV differs from that of 6-MV photon beams by 1.6% ± 0.4%, on the average. By considering the uncertainty of about 2% on all $RE$ values (table 4.1), the conclusion can be drawn that for proton in the range 63 – 230 MeV the response of EBT3 film is not practically different from that of photons, in the same range of absorbed doses, within experimental uncertainties.

As regards the response to carbon ions, figure 4.2-a shows the dose-response relationship for carbon ions in comparison to 6 MV photons; figure 4.2-b shows the corresponding relative dose-response curves as a function of the photon dose, extracted from the calibration curve using the netOD obtained in the films irradiated by ions.
Table 4.2: The fitting parameters obtained from the fitting function (when all data points in figure 4.1-b at the different energies are pooled) and the parameters obtained from the single fitting functions for the relative protons dose-response data.

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Intercept ($a$) and slope ($b$) of the linear fit to the protons response relative to 6 MV photons</th>
<th>Intercept ($a$) and slope ($b$) of the linear fit to the protons response relative to 6 MV photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>$RE = a + b \cdot D$</td>
<td>$a \pm \sigma_a$</td>
<td>$b \pm \sigma_b$</td>
</tr>
<tr>
<td>All energies</td>
<td>0.984 ± 0.004</td>
<td>0.0002 ± 0.0005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fitting Function</th>
<th>Intercept ($a$) and slope ($b$) of the linear fit to the protons response relative to 6 MV photons</th>
</tr>
</thead>
<tbody>
<tr>
<td>$RE = a + b \cdot D$</td>
<td>Intercept ($a$) and slope ($b$) of the linear fit to the protons response relative to 6 MV photons</td>
</tr>
<tr>
<td>63 MeV – CNAO</td>
<td>0.968 ± 0.008</td>
</tr>
<tr>
<td>150 MeV – CNAO</td>
<td>0.992 ± 0.009</td>
</tr>
<tr>
<td>230 MeV – CNAO</td>
<td>0.984 ± 0.009</td>
</tr>
<tr>
<td>150 MeV – HIT</td>
<td>0.994 ± 0.009</td>
</tr>
<tr>
<td>90 MeV – CPT</td>
<td>0.984 ± 0.009</td>
</tr>
<tr>
<td>180 MeV – CPT</td>
<td>0.983 ± 0.009</td>
</tr>
</tbody>
</table>

Table 4.3 contains measured values for the relative dose-response for carbon ions, with the corresponding uncertainty (relative to the data plotted in figure 4.2-b); the data show that the uncertainty of the relative-response $\sigma_{RE}$ for all energies is of the order of 0.02. Table 4.4 shows the fitting parameters obtained from the single fitting functions for the relative carbon ions dose-response data for 115 MeV/u and 400 MeV/u at CNAO; 250 MeV/u at HIT. The curves obtained for carbon ions (figure 4.2-a) show a clear under-response of the EBT3 film over the whole dose range in comparison to 6 MV-photon beams.
Indeed, the relative response of carbon ions is less than unity (at 115, 250 and 400 MeV/u) and shows a different trend for different initial energy of the ions. Hence, it was not feasible to evaluate all the data with a unique linear fit, as was done for the relative response of protons.
Table 4.3 The relative dose-response \((RE)\) with uncertainty, for protons.

![Table 4.3](image)

Table 4.4 The fitting parameters obtained from the fitting function (when all data points in figure 4.2-b at the different energies are pooled) and the parameters obtained from the single fitting functions for the relative carbon ions dose-response data.

![Table 4.4](image)
Hence, considering individual linear fits to each energy dataset (whose results are shown in table 4.4), the conclusion can be drawn that for carbon ions in the range 115–400 MeV/u, the response of EBT3 film is dependent on the initial ion energy and a quenching effect occurs. Furthermore, the under-response is dependent on the initial kinetic energy of the ions.

In conclusion, considering the uncertainty (0.02) on RE values, the measurements indicate that the under-response of the EBT3 film – in the plateau region of the carbon ions Bragg curve – was significant. In particular, the relative efficiency was 0.69 at 115 MeV/u (corresponding to 31% under-response); 0.77 at 400 MeV/u (corresponding to 23% under-response) and 0.86 at 250 MeV/u (corresponding to 14% under-response).

4.2 – *Depth-dose curve in water for protons and carbon ions*

For EBT3 films the dose-response and the corresponding under-response were studied for one monoenergetic beam in proton and carbon ion medical beams respectively. As described in chapter 2, the measurements were performed along the whole Bragg-curve with the EBT3 films immersed in water. The results of the dose measurements with the film were compared with the corresponding measurements obtained with the ionization chamber in the same water tank.

The energy investigated for protons was 150 MeV; the entrance dose value was set to 1 Gy and the peak-to-plateau value for this energy was about 20%. The measurements with EBT3 films and the ionization chamber were carried out at the same depth position along the Bragg-curve, by using a finer sampling in the Bragg peak region. Figure 4.3 shows the depth-dose curves obtained with EBT3 film and with the Markus chamber.
Figure 4.3 (a) The depth-dose curves obtained with EBT3 film and Markus chamber; (b) the same data are replotted only in the region of the Bragg peak, where quenching occurs for the EBT3 film response.

The EBT3 film curve presented a slight under-response in the Bragg peak region. The average ratio of the dose values measured with EBT3 and Markus chamber in the Bragg peak region (150.8 – 151.2 mm) was 0.90 ± 0.04, corresponding to an under-response of about 10%.
The energy investigated for carbons was 400 MeV/u; the entrance dose value was set to 1 Gy and the peak-to-plateau value for this energy was about 30%.

Figure 4.4 shows the depth-dose curves obtained with EBT3 films and with the Markus chamber. Figure 4.4-b shows the same comparison only in the Bragg peak region, where quenching occurs for the EBT3 film response. This demonstrates that the EBT3 film curve
presented an under-response in the Bragg peak region. The average ratio of the dose values measured with EBT3 and Markus chamber in the Bragg peak region (269.2 – 269.6 mm) was $0.58 \pm 0.02$ corresponding to an under-response of about 40%.
Chapter 5.  **Correction methods for the under-response of EBT3 films for hadrontherapy**

As investigated experimentally in this work, and shown in the related literature, the response of the radiochromic film is energy dependent with increasing under-response at low kinetic energies of the ions (protons and carbon ions), where the LET is higher. This implies that – in order to obtain accurate determinations on the spatial distribution of the absorbed dose in tissues exposed to ion beams from dose maps obtained with radiochromic films – suitable correction procedures of the acquired data are necessary, which take into account the observed energy-dependent under-response. Research in this field begun recently, in particular by Italian teams working especially on proton beams at CNAO and INFN-LNS [5,7]. In the following, a description of the two methods will be given.

### 5.1 – Treatment planning system correction procedure

In the study by Gambarini et al. [9], a dose measurement in a configuration of Spread-Out-Bragg-Peak (SOBP) was carried out for the development of the correction procedure; to this purpose, 31 different proton energies and 571 spot position of a pencil proton beam were adopted. Rectangular EBT3 film pieces were placed in the phantom (RW3 tissue-equivalent material) and irradiated with a scanning pencil beam operated by the treatment planning system (TPS) used at CNAO (Syngo RT Planning).

The central depth-dose profile along the direction of the beam was extracted from the measured dose map with the EBT3 film and a profile, along the same axis, was also extracted from the dose distribution calculated by the TPS (figure 5.1).
Figure 5.1 Central SOBP dose profile in water extracted from a dose map measured with an EBT3 film and profile calculated by the Syngo TPS (from ref.[9]).

The intent was to setup a film response correction procedure by using the data extracted from the treatment plan combined with information drawn previously from a very limited number of measurement performed with EBT3 film of the Bragg peaks. For this purpose, three energies were chosen, corresponding to the minimum, average and maximum of the energies involved in the irradiation, respectively. Averaged functions for the depth-dose and under-response curves were evaluated and these functions were suitably translated along the beam axis for calculations.

The software for dose-map correction, developed in MATLAB, utilizes the file extracted from the treatment plan, containing the data of positions, energies and intensities of the proton beams involved in the SOBP. Then, for each energy the authors calculated the depth-dose curve and evaluated the intensity (number of particles) of each pencil beam of the irradiation session.

The software evaluated three profiles, along the axis parallel to the incoming beams (in this case indicated with $x$) where the profile to be corrected was extracted. These profiles were the following:
1. The simulated profile $S_{\text{abs}}(x)$ of the dose assumed to be the one effectively absorbed by the EBT3 film. This evaluation is performed utilizing a Bragg-peak function obtained by averaging the calculated Bragg peaks;

2. The simulated profile $S_{\text{meas}}(x)$ of the dose map assumed to be that measured by the EBT3 film, evaluated as the previous one but utilizing the few measured Bragg peaks;

3. The ratio of the two previous profiles which is considered as a correction profile:

$$R(x) = \frac{S_{\text{abs}}(x)}{S_{\text{meas}}(x)} \quad (5.1)$$

Then, the corrected absorbed dose $D_{\text{abs}}(x)$ is obtained by multiplying the measured dose $D_{\text{meas}}(x)$ by the ratio $R(x)$:

$$D_{\text{abs}}(x) = R(x) \cdot D_{\text{meas}}(x) \quad (5.2)$$

Figure 5.2-a shows the profiles so obtained, together with the measured and calculated profiles. Then, the correction profile was calculated from the ratio of the simulated profiles. By multiplying pixel-to-pixel this profile for the measured one, the corrected dose profile was obtained (figure 5.2-b).

The corrected profile fits well that calculated by the TPS, applied to the case of SOBP in which the dose distribution of the performed irradiation was homogenous. The situation would be different in the case of a non-uniform dose distribution. For this reason the method is still under development.
Figure 5.2 (a) Absorbed dose profile calculated by TPS, measured dose profile and results of the simulations for absorbed dose profile and the measured dose profile; (b) measured dose profile, profile calculated by the TPS and corrected profile (from ref. [9]).

5.2 – FLUKA simulation correction procedure

In the study of Fiorini et al. [5], the dose-response of the EBT3 film was assessed by calibrating the film as dose-to-film (dose-to-EBT3 active layer) and then converting these doses to dose-to-water, after correcting the doses from the film for the under-response. The advantage of this method is that the LET correction is kept independent on the material for which the doses are needed, because it depends only on the active layer material (which will always the same if EBT3 films are used). Simulations of the experimental setup with the Monte Carlo code FLUKA were used to convert the
ionization-chamber dose into film-dose, for the accurate calibration of the EBT3 film. The beam quality correction factor $g_{Q,Q_0}$, determined for EBT2 film [6] is shown in figure 5.3 (the curve for EBT2 film, an old type of the presently available EBT3 film, can be also used for EBT3). It gives a quantification of the necessary correction to apply, in order to account for the film under-response at low energies of protons. It represents the relative effectiveness of the films at the quality $Q$ (protons with the particular used energy) with respect to the effectiveness at the quality $Q_0$ (protons with the energy used for the calibration, in this case 29 MeV). As shown in figure 5.3, the under-response is practically negligible for proton energies higher than 15 MeV. For lower energy irradiations or for irradiations in the Bragg peak region (LET dependence) another calibration is required. Alternatively, in order to use the same function, the quality correction factor $g_{Q,Q_0}$, with $Q$ representing the proton energy beam in use, has to be applied. Then, in the case where a LET correction is required, the energy spectrum of the crossing particles must be known and for this purpose Monte Carlo simulations are necessary.

For the correction procedure, a clamped stack of 25 EBT3 films placed perpendicularly to the beam axis was irradiating using a modulated proton beam. The modulation was adopted to spread the Bragg peak up to half its depth in order to give an almost flat dose distribution across the SOBP. Moreover, the simulated SOBP curve was reproduced with the Monte Carlo code FLUKA. The experimental doses, $d_i$, of the stack, extracted from the uniform regions of interest on each film, $i$, were calculated from the values of their darkening and the calibration function. They were then corrected using the EBT2 correction factor curve.
Figure 5.3 EBT2 beam quality correction factor \(g_{Q_0,0}\) (with \(Q_0\) the calibration protons at 29 MeV) as a function of the energy of the protons crossing the active layer of the film. The blue dashed curve is the parameterised curve of \(g_{Q_0,0}\) determined in Ref. \([6]\) and including the water-to-film stopping power ratio. The red solid curve is the parameterised curve to use in the case of a calibration giving dose-to-film (from ref.[5]).

The average quality correction factors for each irradiated film were calculated using the following expression:

\[
\bar{g}_{Q, Q_0, i} = \frac{\int_{E_{\text{min}_i}}^{E_{\text{max}_i}} f_i(E) g_{Q_0,0}(E) dE}{\int_{E_{\text{min}_i}}^{E_{\text{max}_i}} f_i(E) dE}
\]

where \(i\) represents the region of interest on the \(i\)th film, \(f_i(E)\) the proton spectrum as calculated from the simulations, \(E_{\text{min}_i}\) and \(E_{\text{max}_i}\) respectively the minimum and the maximum energy of the proton spectrum and \(g_{Q, Q_0}\) the fitting function of the quality correction factors. Then, the corrected doses, \(D_i\), were finally calculated by multiplying the correction factor \(\bar{g}_{Q, Q_0, i}\) by the doses calculated from the film darkening, \(d_i\):

\[
D_i = \bar{g}_{Q, Q_0, i} \cdot d_i
\]

(5.3)

(5.4)
Figure 5.4 Reconstructed experimental SOBP created using a 29 MeV proton beam and a modulator. The plotted doses are normalised to the average value of the dose along the flat region of the SOBP. The axis for the average correction $\bar{g}_{0,s}$ (circles and dashed green line) to be applied to the dose obtained from the film darkening (triangles and orange solid line) to calculate the physical dose delivered to the films (squares and blue solid line) is shown on the right side of the graph. As a comparison also the FLUKA simulated doses deposited in the film active layers are shown with circles and red solid line (from ref. [5]).

The resulting reconstruction of the SOBP in the region of interest on the films is shown in figure 5.4, where all the plotted doses are normalized to the average value of the doses along the flat region of the SOBP. The good overall agreement between the simulated data and the corrected experimental doses demonstrates the feasibility of the method used for calculating the final corrected doses.

With this purpose, two studies have been conducted taking one of the lowest and one of the highest therapeutic proton energy configurations attainable at most of the proton therapy facilities and so respectively representing the worst and the best clinical case scenario to show the EBT3 under-response. The low energy scenario refers to an eye treatment involving actively scanned beam energies between 39 and 60 MeV and creating a 1.5-cm thick and 1-cm deep SOBP in water. The high energy scenario refers to a treatment for a target tumor, 5-cm thick and 20-cm deep, involving actively scanned beam energies between 195 and 217 MeV. Results are shown in figure 5.5.
Figure 5.5 Simulated SOBPs created by modulated proton beam energies for (a) an eye treatment (proton energies between 39 and 60 MeV) and (b) a 20 cm deep and 5 cm thick tumor (proton energies between 195 and 217 MeV). The plotted doses are relative to the average value of the dose along the SOBP. The LET corrected dose (blue line and/or squares) from each film active layer, the uncorrected dose (red line and/or triangles) from each film active layer and the average correction \( g_{Q_i, Q_{0,i}} \), green dashed line and circles) to be applied to each uncorrected dose are shown. In figure (b) also the dose deposited in the entire stack (black solid curve) is shown to guide the eye. The maximum corrections are: 1.42 (corresponding to an under-response of 30% for the eye treatment) and 1.08 (corresponding to an under-response close to 7.7% for the high-energy treatment), both required on the tail of the peaks (from ref. [5]).

5.3 – Proposal for a new correction procedure

In this thesis the rationale of a new correction procedure for EBT3 film under-response is proposed, whose experimental verification will be the subject of future work. The idea at the basis of this procedure is that using Monte Carlo simulations validated using calibrated ionization chamber dosimeters, it could be always possible to recover an
accurate dose estimate at any given point in a water phantom. This would be considered as a correction dose value against the biased dose value measured (for a given ion type and incident kinetic energy) with the EBT3 film in that position. The procedure proposed here aims at recovering accurately a dose value corrected for energy-dependent film under-response by using a dataset of correction factors adapted for each particular beam energy and ion type.

First, for protons as well as for carbon ions, one can use a pencil beam of monoenergetic particles incident on a large (e.g. a 30 x 30 x 30 cm³ cubic volume) water volume. The pencil beam, directed along one of the axes of the cube, scans the sample volume at pre-determined incident positions on a square mesh on the entrance surface. At each scan position, for a given ion energy and type, dose determinations via Monte Carlo simulations are made on a 3D mesh of data points (with a variable x-y-z spacing between data point). The set of dose determinations for a given position of the pencil beam will then give the dose Point Spread Function (dPSF) for that ion type and energy. Then, the dPSF is normalized to unit dose at isocenter. For the sake of clarity, figure 5.6 shows a dose map cut along a longitudinal plane of a pencil proton beam in water at 200 MeV obtained with Monte Carlo simulation is shown. Once the normalized dPSF is determined for a given ion energy, the same simulations are repeated for all energies (e.g., 30 different energy values) of interest, as needed e.g. for SOBP scans. Assuming linear superposition of dose distributions produced by a treatment scan with pencil beams of different energies and different intensities, then, for a pencil beam scan of a given entrance area in a treatment scan, the convolution of the pre-determined dPSFs could be calculated for determining the actual 3D dose map in the irradiated volume.
A few numbers of experimental measurements (e.g. minimum, average and maximum energy in the range of interest) with the ionization chamber are necessary for validating the simulations.

For the three energies and at one x-y fixed position on the incident plane, one measurement in the entrance region is necessary as reference: then, one can sample the Bragg peak region with a fine step.

For the determination of the dataset of correction factors, measurements with the EBT3 film will be performed, in the same configuration as for simulations.

As a result of the measurements carried out in this work, the response of the EBT3 film to protons is energy independent in the Bragg plateau region. Hence, after calibrating the EBT3 film at one energy, one can use the resulting calibration curve for the assignment of the dose from the darkening of the film, for each proton beam energy of interest. For the measurement of the under-response in the Bragg peak region, one can use a pencil beam of monoenergetic protons incident on the water tank in a fixed x-y position and perform measurements as a function of depth along the beam direction. A coarser sampling in the entrance plateau region and finer sampling across the Bragg peak, will be adopted.
The set of dose determinations for a given position of the pencil beam will then give the measured dPSF. Once the normalized dPSF is determined for a given energy, the same measurements will be repeated for all energies of interest.

Finally, the dPSF obtained from simulations and that obtained from measurements would give a 3D dataset (in the measurement sample points) of coefficients for correcting the response of EBT3 films.

The same procedure applies for the correction of the EBT3 film response to carbon ions. However, the response of EBT3 to such ions is energy dependent also in the Bragg plateau region. For this region, it is not possible to use a unique calibration curve for all incident energies. As shown in the literature and observed in this work, the relative efficiency of the carbon ions shows an almost constant trend with the dose, for the three energies investigated. Then, it is necessary to perform a dose measurement for all energies of interest and to create a dataset of conversion coefficients relative to a given carbon ion energy. Hence, one can calibrate the EBT3 film with one energy and rescale the dose value for the conversion coefficient at the energy of interest.

At this point, one can follow the procedure previously indicated for protons (dataset of validated simulations and measurement of the film under-response) in order to produce a 3D dataset of correction factors for carbon ions, in the energy range of interest.
Conclusions

Radiochromic films – as high spatial resolution dosimeters – are routinely used for treatment plan verification in conventional radiotherapy (with photon or electron beams), but their use is limited to quality assurance procedures in the case of hadrontherapy with proton or carbon ion beams. This is due to an energy-dependent saturation of the dose response of such dosimeters, in regions where the delivery of dose per unit length by the slowing down ions is high due to the corresponding increase of the ion stopping power.

This thesis, in the line of recent research in this field by groups at major hadrontherapy facilities in Europe, investigated this issue via accurate determinations of the EBT3 film response for the two type ions (protons and carbon ions) and a set of different incident energies. Then, two different correction procedures recently proposed are illustrated; on the basis of these methods and of the extensive set of measurements here produced, the sketch of a new correction procedure is drawn, whose effectiveness will be determined in future work.

The results of the experiments carried out in this work can be summarized as follows.

Protons (63–230 MeV)

The EBT3 film showed the same response for proton beams – in the plateau region of the Bragg curve of the ions – in the range 63–230 MeV as for radiotherapy beams (6–18 MV) (i.e., relative efficiency equal to 1). Then, the performance of the EBT3 film is independent of the incident energy for proton beams. Therefore, the calibration curve obtained for one proton energy can be used for different proton energies in this range (for a given film batch). This is in agreement with recent scientific reports [13], which
investigated the response of EBT films. However, an under-response of the EBT3 film in the Bragg peak region where the proton energy drops to a few MeV was observed. For protons of 150 MeV initial kinetic energy, the average ratio of the dose values measured with EBT3 and Markus ionization chamber in the Bragg peak region (150.8–151.2 mm) was $0.90 \pm 0.04$ corresponding to an under-response of about 10%. This is in agreement with recent scientific reports [18], which investigated the response of EBT films and demonstrated an under-response from 10% to 20% for proton energies in the range of 76-186 MeV.

**Carbon ions (115–400 MeV/u)**

In this thesis an under-response – in the plateau region of the Bragg curve of the ions – was observed for carbon ion beams in the energy range 115–400 MeV/u. This is in agreement with recent scientific reports for EBT films [13]. However, at variance with that previous work, the under-response for carbon ions was dose-independent but energy-dependent, with a relative efficiency of: 0.69 at 115 MeV/u (corresponding to 31% under-response); 0.77 at 400 MeV/u (corresponding to 23% under-response); and 0.86 at 250 MeV/u (corresponding to 14% under-response). These discrepancies are considered statistically significant, taking into account the uncertainty of 0.02 on the relative efficiencies. In particular, the extent of the under-response has a non-monotonic dependence on the ions’ initial energy. This observation demonstrates a complex phenomenon for the incident energy and LET dependent of the response of such radiochromic film to high-energy ion beams, which calls for complex procedures for the correction of EBT3 films.
The performance of the EBT3 film is dependent on the incident energy for carbon ions, in the range 115-400 MeV/u. For this reason, separate calibration curves should be obtained for different carbon ion energies, with EBT3 films. Moreover, as for protons, there was an under-response of the EBT3 film in the Bragg peak region, in agreement with the literature [10, 12]. For carbon ion beams of 400 MeV/u, the average ratio of the dose values measured with EBT3 and Markus chamber in the Bragg peak region (269.2–269.6 mm) was 0.58 ± 0.02 corresponding to an under-response of about 40%.

As a concluding remark, this work sets forth the idea that a suitable strategy for correcting the observed under-response is via the combined use of Monte Carlo simulation (with the use of a calibrated ion chamber for the accurate dose determination for Monte Carlo validations) for the ion transport in matter and EBT3 film measurements.
References


Acknowledgments

Firstly, I would like to express my sincere gratitude to my tutor Prof. Paolo Russo for the continuous support he gave me during my MSc career and consequent thesis work. I thank him for his patience, motivation, and immense knowledge. We met when I asked his collaboration for my bachelor’s degree final thesis; his guidance helped me all the time during my career and especially while I was writing my manuscript. I could not have imagined having a better mentor for my university career and my personal growth. Prof. Russo, thank you for trusting me and giving me the opportunity to work on such an interesting issue beyond all possible difficulties.

The experimental work in this thesis has been carried out with the fundamental support of the main research and clinical centers for radiotherapy, who granted beam time at their accelerator facility. It has been greatly rewarding for me to work with the groups at these centers where I received a warm welcome, full support in a friendly atmosphere.

I thank in particular the following persons:

Dr. S. Rossi, Dr. M. Ciocca and Dr. A. Mirandola (CNAO, Pavia Italy);

Dr. R. Calandrino, Dr. C. Fiorino, Dr. C. Sini and Dr. S. Broggi (San Raffaele Hospital, Milano Italy);

Prof. O. Jaekel, Dr. M. Martisikova and Dr. G. Arico (HIT, Heidelber Germany);

Dr. M. Amichetti, Dr. M. Schwarz and Dr. F. Fracchiolla (CPT, Trento Italy).