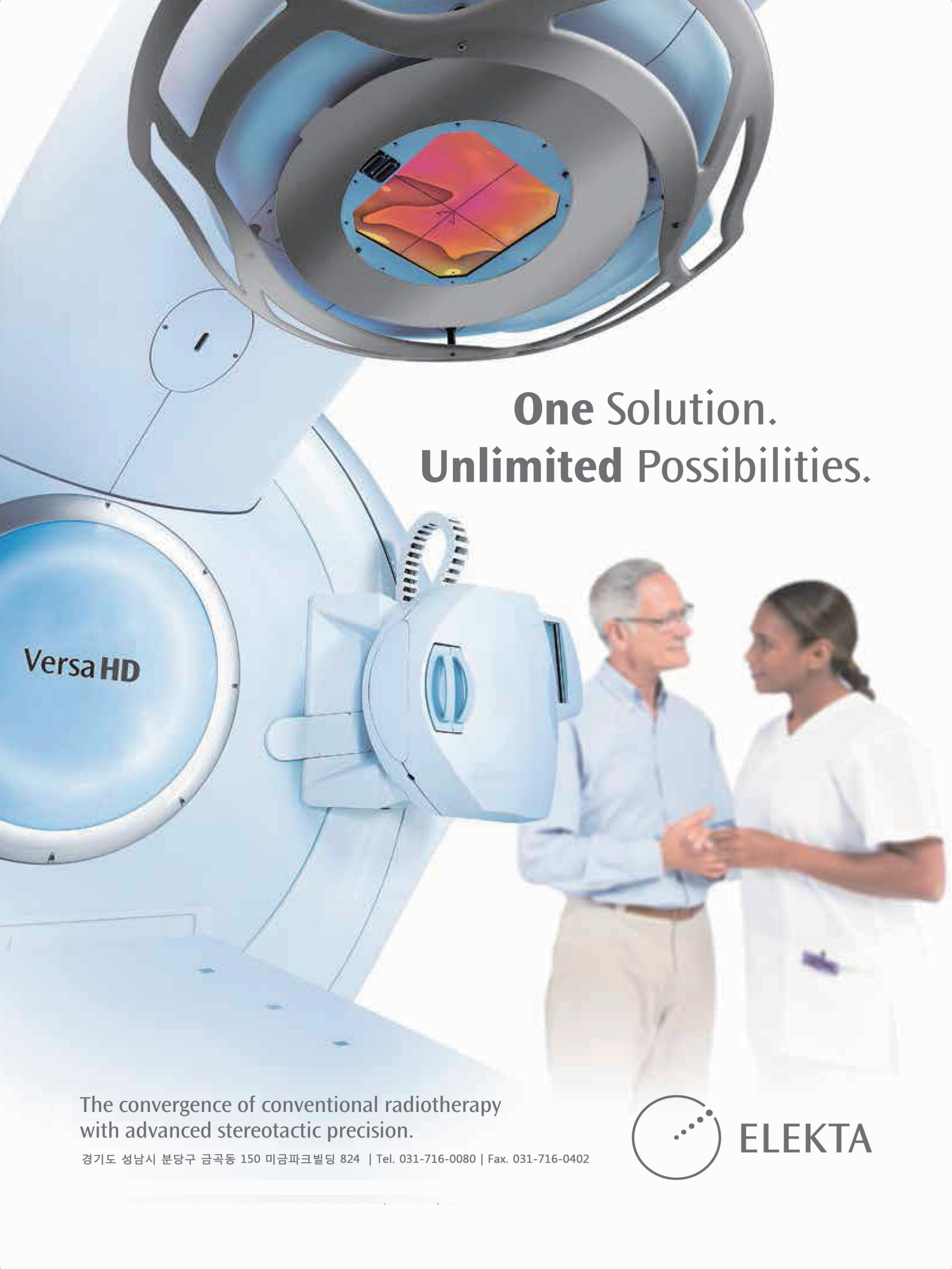
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Measurement of Proton Beam Dose-Averaged Linear Energy Transfer Using a Radiochromic Film

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Purpose: Proton therapy has different relative biological effectiveness (RBE) compared with X-ray treatment, which is the standard in radiation therapy, and the fixed RBE value of 1.1 is widely used. However, RBE depends on a charged particle's linear energy transfer (LET); therefore, measuring LET is important. We have developed a LET measurement method using the inefficiency characteristic of an EBT3 film on a proton beam's Bragg peak (BP) region.
Methods: A Gafchromic EBT3 film was used to measure the proton beam LET. It measured the dose at a 10-cm pristine BP proton beam in water to determine the quenching factor of the EBT3 film as a reference beam condition. Monte Carlo (MC) calculations of dose-averaged LET (LET_d) were used to determine the quenching factor and validation. The dose-averaged LETs at the 12-, 16-, and 20-cm pristine BP proton beam in water were calculated with the quenching factor.
Results: Using the passive scattering proton beam nozzle of the National Cancer Center in Korea, the LET_d was measured for each beam range. The quenching factor was determined to be 26.15 with 0.3% uncertainty under the reference beam condition. The dose-averaged LETs were measured for each test beam condition.
Conclusions: We developed a method for measuring the proton beam LET using an EBT3 film. This study showed that the magnitude of the quenching effect can be estimated using only one beam range, and the quenching factor determined under the reference condition can be applied to any therapeutic proton beam range.

Keywords: Proton therapy, Linear energy transfer, Film dosimetry, EBT3

Introduction

Proton therapy is commonly used as a radiation treatment for patients with cancer because of protons' specific energy transfer property, which reduces an absorbed dose at normal organs, called the Bragg peak (BP) specification. To estimate the biological effects of proton therapy, the relative biological effectiveness (RBE), which is the quantity of the relative biological effect compared with ^{60}Co gamma-ray, is used and treated as a constant value of 1.1. However, RBE is related to linear energy transfer (LET) and varies according to the proton beam energy because of energy loss straggling and secondary ion emission. Moreover, a study reported the destruction of normal tissues at the end of the spread-out BP because RBE increased in that region [1]. Therefore, a variable RBE model was developed to reflect these effects, which is based on the dose, dose-averaged LET (LET_d), and tissue-specific parameters [2]. Consequently, measuring the LET_d for the proton therapy is helpful because the variable RBE model can be implemented into the treatment plan from this measurement.

LET_d is measured using a radiochromic film. A radiochromic film is a valuable tool for measuring 2D dose distribution with a high spatial resolution that is less than submillimeter [3]. The film measures the dose distribution via a magnitude of discoloring itself to black when the film is exposed to a proton beam. However, in the depth region of the proton beam having high LET, the film's responses are underestimated, which is called quenching [4]. In this study, a Gafchromic EBT3 film (Ashland, NJ, USA) was used, which is commonly used as a dosimetry tool. The Gafchromic EBT3 comprises a 28-μm active layer sandwiched between two 125-μm matte-polyester substrates and has a 25-μm high spatial resolution. The quenching effect of the EBT3 film in measuring the depth dose profile was reported by several studies [5,6].

Several studies corrected the discrepancy between the depth dose curve measured by the radiochromic film and that measured by an ion chamber. For example, a third-order polynomial fitting model corrected these underestimated dose curves of the proton beam [3]. Similarly, through a second-order polynomial fitting model, the dose curves and LET were corrected and calculated in the carbon ion beam [7]. Additionally, the LET dependency was corrected using the exponential model for dynamically scanned proton beams [8]. These studies used the LET values obtained using Monte Carlo (MC) calculations for each particle energy beam range [7-9].

This study reported the measurement method and results of the LET_d using the aforementioned Gafchromic EBT3 film. The film was placed in a water phantom via a structure made by a 3D printer and irradiated with the passive scattering proton beams generated by a proton cyclotron of the National Cancer Center Korea (NCCK). Then, the ratios between the measured doses and that measured by the Markus chamber were calculated, and a parameter mediating between the LET_d and ratio was estimated. The parameter was estimated under a reference beam condition by fitting the ratio to the LET_d obtained using MC calculations. This parameter was finally applied to the other test beam cases to measure the LET_d.

Materials and Methods

1. Concept of LET measurement

To describe a particle's energy spectrum as a single-valued metric, the averaged LET is commonly used. For example, the linear-quadratic RBE model uses two parameters α and β to represent the radiosensitivity in radiobiology; they depend on the averaged LET. Historically, the averaged LET is calculated in two ways: track-averaged LET and LET_d. This study focused on the LET_d because the LET_d is commonly used when describing radiation biology, clinical practice, and dosimetry. This LET_d is defined as the average value weighted by each single charged particle i, and it is given by the following equation:

$$LET_d = \frac{\sum_i \mathrm{d}_i \cdot LET_i}{\sum_i d_i} \quad (1)$$

where d_i is the microscopic dose in an infinitesimal volume from a single particle [10].

Birk's equation, which is commonly used to describe the quenching effect of a scintillator, was applied to the EBT3 film. The definition of Birk's equation is as follows:

$$\frac{dS}{dr} = \frac{A\, dE/dr}{1+kB\, dE/dr} \quad (2)$$

where S is the number of fluorescent quanta, r is the residual range, dE/dr is the stopping power, kB is the quenching factor, and A is a constant of proportionality [11]. The parameters A and kB are determined through experiments. In the therapeutic proton beam having energy larger than 10 MeV, the stopping power is high enough to be directly proportional to the number of fluorescent quanta per unit length if there is no quenching effect (kB=0). For that reason, the stopping power is directly converted to the radiation dose with a normalization parameter. In contrast, if the quenching factor is not zero, the number of fluorescent quanta decreases proportionally to the quenching correction factor (QCF) given by the following equation [12]:

$$QCF=1+kB\,dE/dr \tag{3}$$

Therefore, the underestimated dose can be corrected by multiplying the QCF, which is given by the follow equation:

$$D=k'\cdot\frac{dS}{dr}\cdot QCF=D_{under}\cdot QCF \tag{4}$$

where k' is a normalized factor and D_{under} is the underestimated dose from the light yield. Because the stopping power can be replaced by LET in the therapeutic proton beam, the LET can be calculated using Equations (3) and (4). It is given by the following equation [13]:

$$LET=\frac{1}{kB}\cdot\left(\frac{D}{D_{under}}-1\right) \tag{5}$$

In this equation, the corrected dose D can be replaced by the dose measured by the ion chamber, which is a standard dosimeter, because it means the dose without the quenching effect. Furthermore, in this study, the underestimated dose D_{under} from the scintillator is replaced by the dose measured by the EBT3 film.

In this study, we assumed that the aspects of the quenching effect of the film and that of the scintillator are similar. However, the quenching effect of the film decreases from the distal fall-off region, observed in a previous study, and the quenching effect is less effective in the plateau region [3]. Therefore, the LET is measured only from 70 percentage depth dose (PDD) region before the distal fall-off region on the EBT3 film. Because kB must be determined by the observation before measuring the LET, it was estimated under the reference beam condition using the LET_d obtained by MC calculations. To obtain the kB, the corrected dose D was measured by the ion chamber and the underestimated dose D_{under} was measured by the film; then, they were fitted to the LET obtained by MC calculations using the least χ^2 fitting method. The determined kB was applied to the other test beam cases.

2. MC calculation of LET_d

The MC tool TOPAS was used to calculate the LET_d and physical doses [14]. A study designed and calibrated the proton beam nozzle structure [15]. Its beam parameters are determined by the converting algorithm (ConValgo) provided by the Proteus 235 manufacturer, IBA (Louvain-la-Neuve, Belgium). Nozzle simulation was performed to match the experimental environment as similar as possible. When primary protons were generated from the beam source, they passed through the nozzle structures, for example, beam scatterer and range modulator. The phantom material was set to G3_WATER with dimensions of 30×30×30 cm^3. The physical dose and LET were derived from the water phantom with a 1-mm interval and beam direction. The simulation dose profile distributions agreed with the measured dose profile from the Markus chamber (Fig. 1).

3. Radiochromic film measurement

Proton beams for the film measurement were irradiated by IBA Proteus 235 in NCCK. This machine provides energy proton beams ranging from 70 to 230 MeV with a full field size of 40×30 cm^2. The passive scattering mode was used for the irradiation. The pristine BP 10-cm proton beam in water was used as a reference beam, and the pristine BP 12-, 16-,

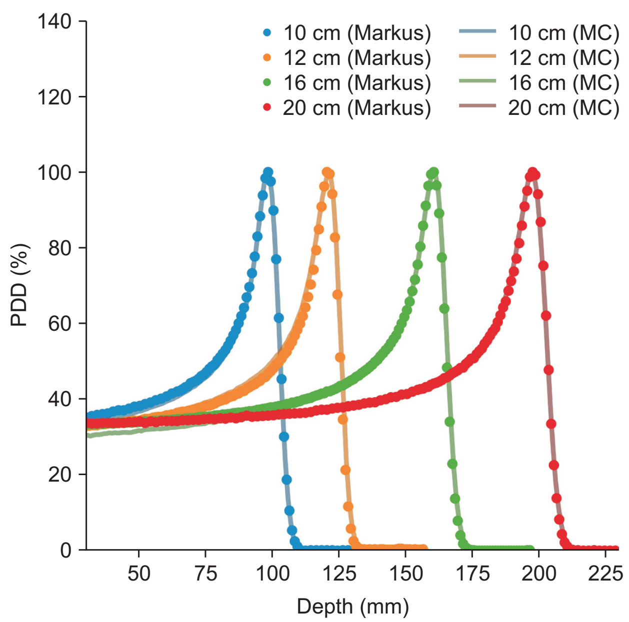

Fig. 1. Data and MC comparison of depth dose curves of 10-, 12-, 16-, and 20-cm water equivalent range beams measured by the Markus chamber (point plots) and MC (solid lines). MC, Monte Carlo; PDD, percentage depth dose.

and 20-cm proton beams in water were used as test cases. The detailed conditions are shown in Table 1. Advanced Markus Chamber PTW 34045 was used as a reference chamber to determine these pristine BP ranges of proton beams and measured the PDD in the water phantom.

EBT3 films (Lot 01042104) were irradiated in a water phantom and were fixed in the water phantom using a structure made by a 3D printer (M300 plus; Zotrax, Olsztyn, Poland). The structure comprises two plates with an open center, and the film was placed between the two plates. Then, the film was fastened by tightening plastic screws in the plates. A diagram of the structure is shown in Fig 2b. Moreover, to avoid perturbations if the film was parallel to the proton beam path, the inside of the plates was placed on a 2.4° inclined plane [8]. Because the film was tilted by the plates, the tilted depth was corrected as follows:

$$d_{corrected}=d\cdot\cos(2.4°) \tag{6}$$

where $d_{corrected}$ is the corrected depth and d is the tilted depth. The entire measurement system is shown in Fig. 2c.

The irradiated films were scanned using a commercial 48-bit-color scanner (Epson 10000XL scanner; Epson, Nagano, Japan), which has spatial resolution of 0.353 mm and estimated radiation doses through an image process. The scanned film images were analyzed using RIT (RIT, CO, USA). The only red channel was read even though the images consisted of three colors: red, green, and blue. The median filter with a kernel size of 5 was applied to remove impulse noise in the image. The pixel values given by the image process were converted using a calibration curves.

To convert the darkness of the pixel value to the radiation dose, the calibration curve was created using a proton beam having a pristine BP 13.89 cm in water. The EBT3 film was placed after a solid water phantom, which had a 3.135-cm water equivalent, and radiation doses were measured from 0 to 1,000 cGy using films. The interval of data points

Table 1. Reference and test beam conditions in this study

Beam range	Field size (cm×cm)	Beam energy (MeV)	Beam current (nA)
Reference beam condition			
10 cm	10×10	172	70
Test beam conditions			
12 cm	10×10	162.14	70
16 cm	10×10	185.00	70
20 cm	10×10	205.2	70

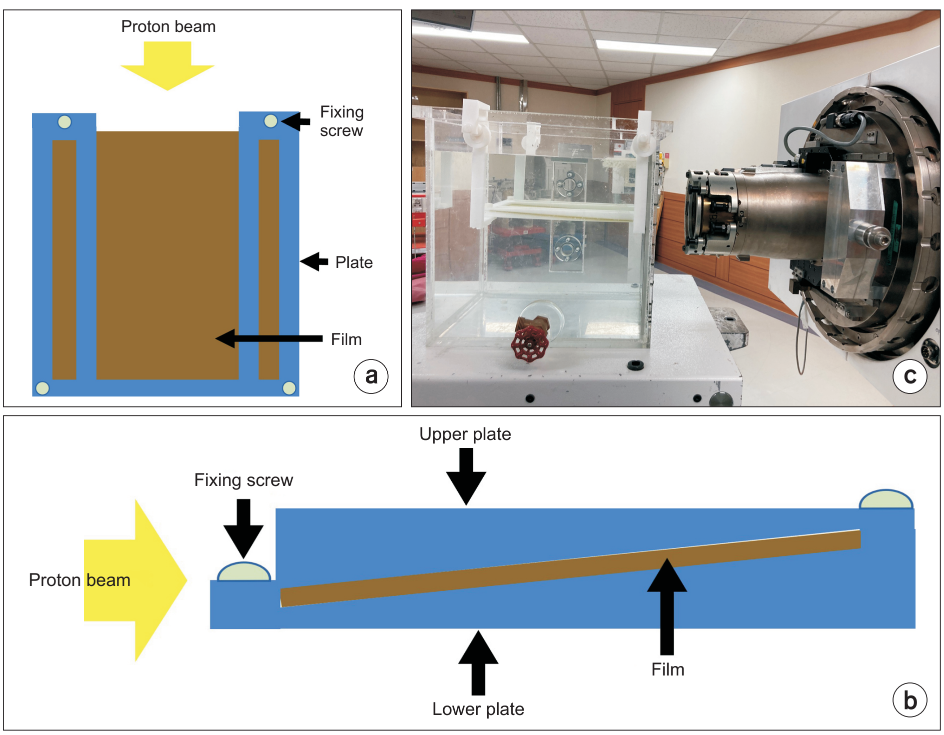

Fig. 2. (a) Top view of a schematic diagram of the measurement system, (b) side view of the 3D printed structure, (c) side view of the measurement system.

was interpolated by cubic-spline interpolation, which is constructed from third-order polynomials passing through two points, and the calibration curve was estimated (Fig. 3).

Results

Fig. 4 shows the results of the reference beam condition. In Fig. 4a, points indicate the PDD curve measured by the EBT3 film, and the solid line indicates the PDD curve measured by the Markus chamber. They were normalized to the percent dose by converting the Markus' top of BP to 100%. The comparison between the measurement results of the EBT3 film and those of the Markus chamber was described as a ratio curve, expressed as a dashed line. The film responses were almost the same as the Markus chamber responses in the plateau region; however, the film responses decreased compared with that of the Markus chamber in the BP region and then increased again as it went to the distal fall-off region. Fig. 4b shows the estimated LET_d under the reference beam condition (the dashed line) and the LET_d obtained by MC calculations (the solid line). The kB was estimated using the least χ^2 fitting to Equation (5) with this ratio plot and the MC calculation of LET_d as the input values. The estimated kB was 26.15±0.08. The uncertainty was only considered when the fitting uncertainty was 0.08 (0.3%).

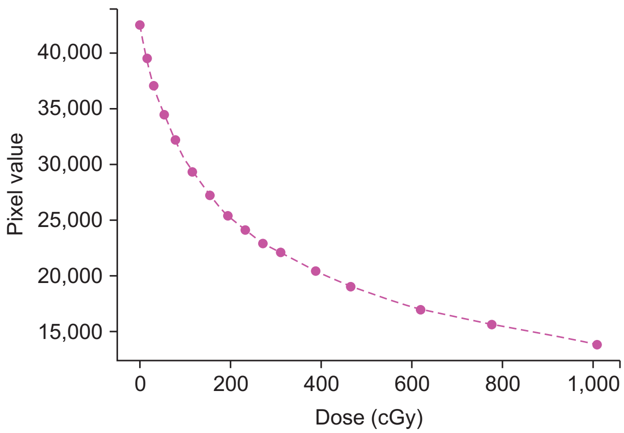

Fig. 3. EBT3 film calibration curve. Data points are measured behind the 3.135-cm solid water phantom.

Based on the kB determined under the reference beam condition, the dose and LET_d were measured in the 12-, 16-, and 20-cm proton beams in water, called test beam conditions (Fig. 5). For each beam condition, the PDD curves measured by the EBT3 film and Markus chamber are shown in Fig. 5a. The curves were normalized in the same way as that under the reference beam condition. Fig. 5b shows the response of the EBT3 film to that of the Markus chamber ratio about the LET_d. The ratio curves, represented as a point plot for test beam conditions, are compared with the ratio curve of the reference beam condition, represented as a solid line. The ratio curves from 2 to 7 keV/μm LET_d of all beam conditions decreased and increased in the region of 7 keV/μm or more. The aspects of the curves looked similar; however, the detailed ratio values are not same. Nevertheless, the kB approach was applied to the test beam conditions.

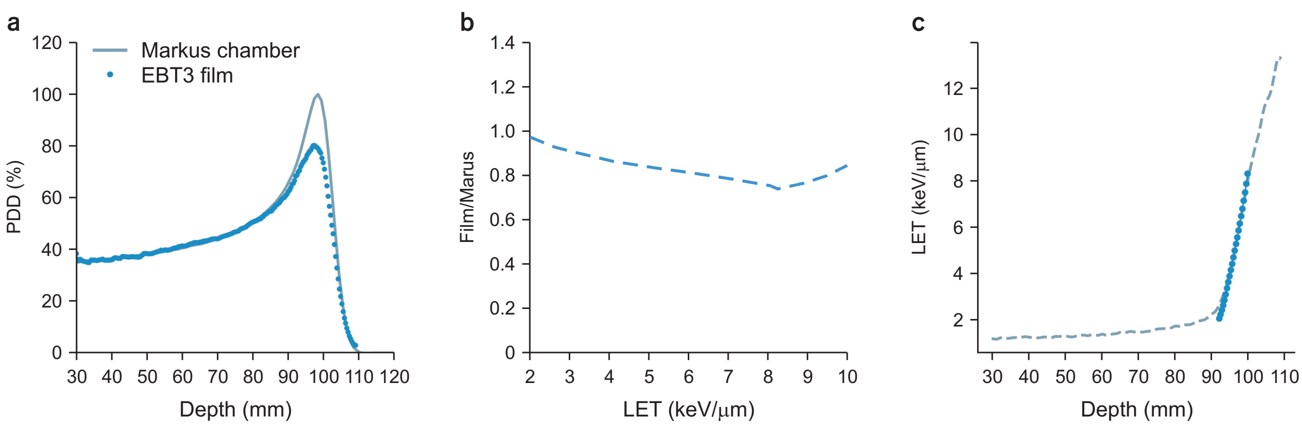

Fig. 4. Under the water equivalent range 10-cm reference beam condition, (a) comparison of PDD curves measured by the EBT3 (point plots), and the Markus chamber (solid line), (b) the response ratio of the EBT3 film to the Markus chamber about LET_d (c) comparison between estimated LET_d (point plot) and LET_d calculated by MC (solid line). LET, linear energy transfer; MC, Monte Carlo; PDD, percentage depth dose.

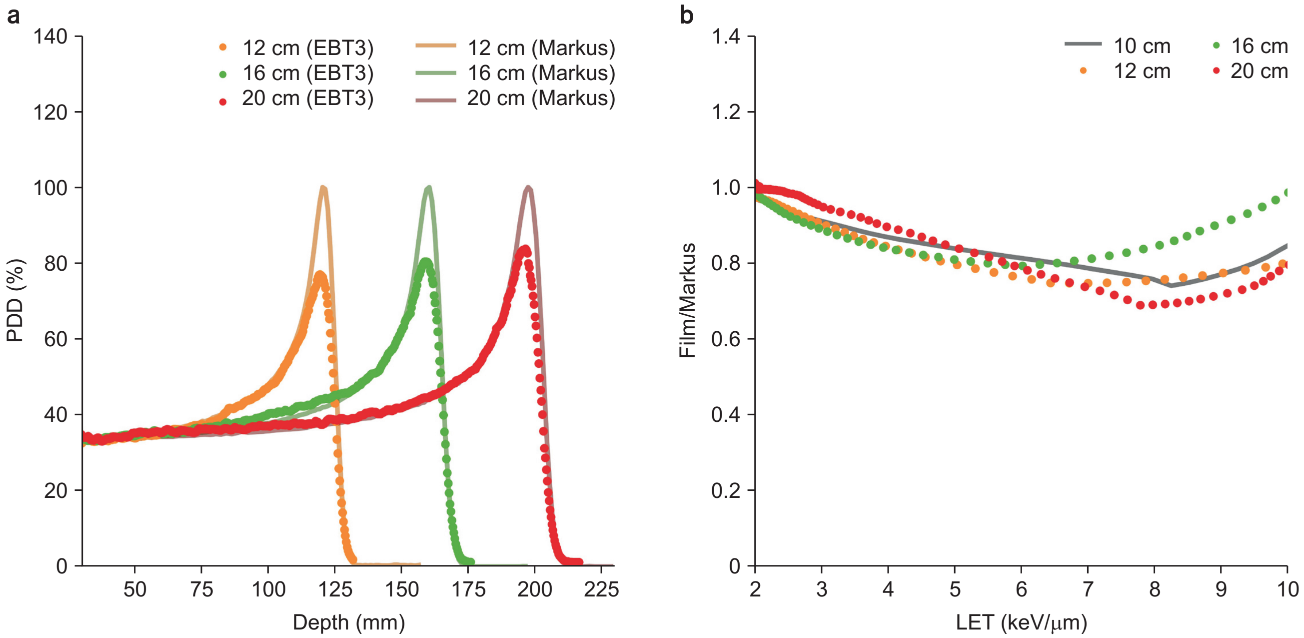

Fig. 5. In the water equivalent 12-, 16- and 20-cm beam ranges, (a) PDD curves measured by EBT3 (points) and the Markus chamber (solid lines), (b) the response ratio of film to Markus about LET_d. LET, linear energy transfer; PDD, percentage depth dose.

For example, the ratios of the percent dose at the midpoint between 70% PDD and the top of the BP for each beam condition were 0.846, 0.849, and 0.869, respectively, and the measured LET_d were 4.776, 4.650, and 3.930 keV/μm, respectively. Discrepancies between the measured LET_d and the MC calculations were 0.809, 0.905, and –0.579 keV/μm. The full results are shown in Fig. 6. Because the aspects of the ratios of the responses of the test beam conditions were different from those under the reference condition, discrepancies increased when the beam range increased.

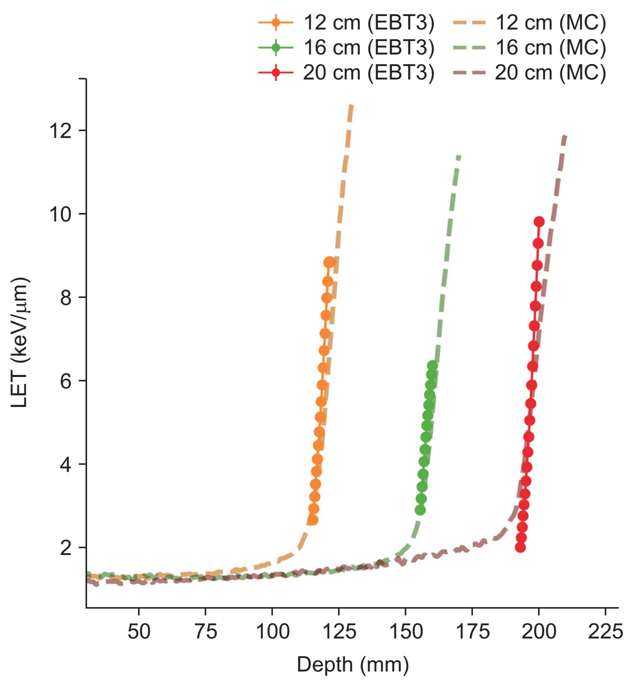

Fig. 6. Measured LET_d (points) of water equivalent 12-, 16-, and 20-cm beam ranges, they were compared to LET_d calculated by MC (solid lines). LET, linear energy transfer; MC, Monte Carlo.

Discussion

In this study, LET_d measurements using an EBT3 film were attempted with the quenching factor (kB) determined under a single beam condition. The percent dose response of the EBT3 film was approximately 20% smaller than that of the Markus chamber at the top of the BP, which coincides with the results of another study [6]. Furthermore, the considered uncertainty was 0.3%, which is well within the realms of acceptability. However, the measurement was only valid at the start point (70% of the PDD region) to the top of the BP region because there was no quenching effect on the plateau region, and the aspect of the quenching effect was different from that of the scintillator [13]. However, this study showed the feasibility of LET_d measurement using a radiochromic film via Birk's equation, which is widely used to measure the quenching effect in the scintillator. The LET_d correction or measurement studies used MC calculations for each beam range to estimate the LET_d; however, the study showed that MC calculations are not needed, unless calculating the quenching factor is required [6,8].

Although the goals of this study were to use EBT3 films through Birk's equation to develop and measure the LET_d, this approach can be used in a restricted region. The restriction exists as the magnitude of the film's quenching effect is different from that in the scintillator, which is not computable using Birk's equation. The average ratio of the EBT3 percent dose to the Markus percent dose for each beam condition is similar to the average ratio under the reference beam condition (80%). However, the LET_d in the long-range beam had discrepancies with the MC calculation. Therefore, the characteristics depend on the beam range: energy loss straggling and secondary ion emission should be considered in the fitting formula.

Conclusions

We developed a method for measuring proton beam LET using an EBT3 film. Although the aspects of the depth dose were different for each beam condition, the film can be a useful tool for LET measurements. Additionally, this study showed that the magnitude of the quenching effect can be estimated by only one beam range, and the same quenching factor (kB) can be applied to any therapeutic proton beam range.

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Conflicts of Interest

The authors have nothing to disclose.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

Author Contributions

Conceptualization: Soonki Min. Data curation: Seohyeon An. Formal Analysis: Seohyeon An. Funding acquisition: Se Byeong Lee. Investigation: Seohyeon An, Sangil Pak, Seonghoon Jeong, Soonki Min, Dongho Shin, Youngkyung Lim, Jong Hwi Jeong, and Haksoo Kim. Methodology: Seonghoon Jeong. Software: Seohyeon An. Supervision: Tae Jeong Kim and Se Byeong Lee. Writing – original draft: Seohyeon An and Sangil Pak. Writing – review & editing: Seonghoon Jeong and Se Byeong Lee.

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