Simulation of dose enhancement in radiotherapy caused by cisplatin

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Abstract: This research considers potential dose increase in a target due to cisplatin (Pt) concentration and radiation type. Dose changes were calculated with cisplatin concentrations from 0.003 to 120 mM. Monte-Carlo simulation of Linear accelerator (Elekta Synergy) and X-ray tube (Xstrahl300) was carried out using Geant4 and PClab. At the first stage of this research, we performed a simulation of energy spectrum from radiotherapy units (spectrum model). The next stage was the modeling of a linear accelerator head and an X-ray tube, and the dose distribution in the water phantom (PDD model). At the second stage, dose changes were investigated in the presence of cisplatin in the target (CIS model). The simulation results showed that the dose escalation can be caused by photon-capture therapy (PCT). There is a dose enhancement in the volume where cisplatin is accumulated. However, the photon energy increase from 60 to 250 kV and the increase of the target depth reduces the effect of PCT due to the decrease of the photoelectric effect cross-section. It should be noticed, that the orthovoltage X-rays energy, listed in the table with results, shows higher dose enhancement, than the megavoltage photon beam generated from linear acceleration sources. In addition, the dose enhancement factors (DEF) are higher in a linac without a flattening filter, than in a linac with a flattening filter.

Keywords: Accelerator modelling and simulations (multi-particle dynamics; single-particle dynamics); Avalanche-induced secondary effects; Detector modelling and simulations I (interaction of radiation with matter, interaction of photons with matter, interaction of hadrons with matter, etc); Radiotherapy concepts

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https://doi.org/10.1088/1748-0221/15/06/C06061
1 Introduction

Radiation therapy is an important and effective option for the treatment of malignant tumors [1]. Actual problems of radiotherapy are increasing the effectiveness of treatment (decreasing the survival rate of cancer cells) and reducing side effects (minimizing the dose to sensitive normal tissues and organs). Binary technologies of radiation therapy can be used to improve treatment results. One of the most promising technologies is contrast-enhanced or “photon-capture” radiotherapy (PCT) [2]. The basic principle of PCT is generation of characteristic X-rays and low-energy Auger-electrons due to the interaction between photons and atoms of heavy elements (Z ≥ 53). In a biological tissue this secondary low-energy radiation ionizes cancer cells structures (e.g. DNA and RNA). In addition to this, the secondary radiation ionizes nearby water atoms and leads to the occurrence of highly active radical series, which causes destruction of the macromolecules of DNA and RNA as well as other cell structures.

Unlike megavoltage photons, lower energy X-rays have more pronounced dosimetric effects (DEF) due to the domination of photoelectric effect (up to about 200 kV) [3]. Accordingly, the energy escalation of photon beams also leads to a gradual decrease of the effect of PCT. However, low-energy photons for medium- and deep-seated tumors are limited due to their low penetrating ability. But, these orthovoltage X-rays energy can be used in intraoperative therapy or in the treatment of superficial lesions. Megavoltage X-rays from linear accelerators are widely used to treat deep-seated tumours, where the Compton effect is maximal and the photoelectric effect is minimal. Although the effect of PCT should be low, but different studies show the escalation of energy in the target volume due to the introduction of dose-enhancing agent (DEA) under megavolt
photon beams [4–6]. Some authors suggest that the observed dose increase is caused by the wide energy spectrum of photon beams, which includes the low-energy kilovolt energy range.

In this study the chemotherapeutic drug cisplatin (C\textsubscript{12}H\textsubscript{6}N\textsubscript{2}Pt), which contains platinum atoms, was taken as DEA. Cisplatin is one of the most effective cytotoxic widely used drugs in the treatment of malignant tumors, which kills cancer cells by damaging DNA and inhibiting DNA synthesis [7]. Cisplatin causes DNA damage by the formation of inter- and intrastrand adducts. The cisplatin-DNA adducts can cause the cell cycle arrest, inhibition of DNA replication and transcription, and eventually apoptosis i.e. cell death [8]. In addition to the effects at the intracellular level, it is now recognized that cytotoxic events caused by cisplatin can begin at the plasma membrane level, where it directly interacts with proteins and lipids, causing changes in the membrane structure and biophysical properties. Such changes can affect cell signaling events, which lead to the death of cancer cells [9]. Cisplatin-based chemotherapy has been demonstrated to improve local control, disease-free survival, organ preservation, and overall survival of patients with cancers of the testis, ovary, cervical, bladder, lung, head and neck [10]–[13]. In addition, cisplatin, typically in combination with etoposide and bleomycin, shows outstanding efficacy in the treatment of testicular cancers where the regimens including this drug afford cure rates of greater than 95%. The effectiveness in the treatment of other cancers is more limited due to acquired or intrinsic resistance. The mechanisms contributing to cisplatin resistance can be divided into four categories: decreased drug uptake, increased DNA repair, defects in apoptosis pathways, activation of pro-survival pathways or inhibition of pathways that promote cell death [14].

Chemoradiotherapy with cisplatin demonstrates not only a radiobiological effect (Survival Enhancement Factor — SEF), but also obvious dosimetric effects (Dose Enhancement Factors—DEF) in a tumor [15, 16]. The effectiveness of chemoradiotherapy with cisplatin in a tumoral model showed a significant reduction of the tumor volume was received after the tumor irradiation by 150 kV X-rays at a dose rate of 2.5 Gy/day (20 days). Authors noted, that the chemoradiotherapy-treated tumoral cells with chemoradiotherapy lost their capability to form colonies and reproduce themselves [17]. Also, clinical trials in studies of the brachytherapy of breast carcinoma confirmed tumor growth retardation in mice with the introduction of platinum ions and x-ray irradiation [18]. There is a significant increase in cell death when considering radioresistant tumors under cisplatin chemoradiotherapy and tumor irradiation by 77.4 kV and 79.4 kV [19].

In this research, we simulated the DEA concentration/DEF dependence at 6 and 10 MV medical linac and orthovoltage X-rays radiation using Monte-Carlo simulation by the means of Geant4 and PClab.
2 Materials and methods

2.1 Clinical dosimetry

The percentage depth dose (PDDs) curves were measured for 6 and 10 MV linear accelerator (Elekta Synergy, Elekta Ltd.) and X-ray tube (Xstrahl300) with energy 60, 120, 180 and 250 kV (figure 1). The PDDs in a water phantom (Blue Phantom, IBA) were measured from Linear accelerator using ionization chamber 0.13 cc CC13 (IBA). The source-surface distance (SSD) was 100 cm, the radiation field area was $10 \times 10$ cm$^2$. Dose measurements in the energies range from 100 kV to 250 kV using ionization chamber 0.40 cc PPC40 (IBA) were carried out. The 60 kV energy using the SP34 QA phantom and farmer chamber 0.02 cc PTW23342 was measured. Dose measurements in water phantom by 1 mm increments from linac and X-ray tube were conducted.

2.2 Monte-Carlo simulation

Monte-Carlo simulation was carried out using Geant4 version 10 [20] and PClab version 9.9 [21] codes to perform the dose calculation in this research. At the first step of this research we performed simulation of energy spectrum from radiotherapy units (section 3.1). The next step is the modeling of dose distribution in the water phantom (section 3.2) from linear accelerator head and X-ray tube. At the second stage, dose changes in the presence of cisplatin in the target (section 3.3) were investigated. A total of $1 \times 10^8$ histories were run in the model’s calculation and the statistical uncertainty of the simulation was kept less than 1%.

2.3 Medical linac simulation

Figure 2a shows the spectrum model structure considered in this study. Simulated components included: source of electron beams, X-ray target 1 mm thick, copper holder below the target 4 mm thick and sensitive detector 1 nm thick. The source in the vacuum space was modeled. The electron beam was 2 mm in diameter. The tungsten target was bombarded by an electron beam with certain energy to produce photon beam. The incident electron beam with a mean energy of 6.7 MeV and Gaussian energy spread of 0.2 MeV for nominal 6 MV energy photon beam was used. The dimensions of focal spots of 3.0 mm in the crossline direction. The corresponding values were 10.4 MeV, 0.3 MeV and 3.0 mm for the 10 MV energy photon beam.
Based on the manufacturer specifications, we simulated the head of the medical linear accelerator Elekta Synergy located at the Tomsk Regional Oncology Centre. Figure 2b presents the head structure of the linear accelerator considered in this study (PDD model). Simulated components included: X-ray target, Primary conical collimator, X-ray beam flattening filter, ionization chamber, thin mylar mirror, Multi-Leaf Collimator (MLC), Asymmetric jaws.

The distance between the accelerator source and the water phantom surface (SSD) was 100 cm. Square field $10 \times 10 \text{ cm}^2$ were studied. The voxel size of sensitive detector was $0.5 \times 0.5 \times 0.1 \text{ cm}^3$. The code of PDD simulation for medical linear accelerator was calculated for filtered and flattening filter free (FFF) systems. The removal of the flattening filter leads to a radially decreasing fluence distribution and thus to inhomogeneous dose distributions. The advantage of this method is considerable increase in the dose rate, thus reducing treatment time. Moreover, the flattening filter system absorbs low-energy photon beam, while the FFF system transmits more of the number of low-energy photons capable of a photoelectric effect. This method is actively used across a number of treatment modalities, including radiosurgery, tomotherapy, IMRT, volumetric modulated arc therapy (VMAT) and stereotactic body radiation therapy (SBRT) [22].

2.4 X-ray tube simulation

As a result of the interaction between beams of primary particles (electrons) and the tungsten anode of the X-ray tube, bremsstrahlung and characteristic radiation is generated. The energy spectrum of X-ray photon beams in detector 1 nm thick was calculated. Figure 3a shows a simulation of the generating x-ray photons (spectrum model). The electron beam is a multidirectional point source and its diameter is equal to 2.00 mm. The anode is located at an angle of 20 degrees. The model includes a beryllium window 2 mm thick. The interaction of X-ray photons and water was simulated to obtain data on depth-dose distributions at the second stage. Figure 3b shows a simulation of PDD in water phantom (PDD model). The model includes primary filters as a half-value layer (HVL), additional filter of various thicknesses, conical applicator and water phantom.

Percent depth dose with sensitive ring detector was defined 1 cm radius and 1 mm thick. The PDD with a 1 mm step were scored using detector inside a water phantom with dimensions of $41 \times 47 \text{ cm}^2$. The distance from the radiation source to the phantom surface was 50 cm for energy of more than 100 kV and 30 cm for energy of up to 100 kV. The radiation field with a transverse size of $10 \times 10 \text{ cm}^2$ was used.
The graphic images of the models are presented in figure 4 for Xstral300 X-ray tube and figure 5 for Elekta Synergy linear accelerator.

![Figure 4](image1.png) ![Figure 5](image2.png)

**Figure 4.** The graphic image of Xstral300 simulation.

**Figure 5.** The graphic image of Elekta Synergy simulation.

### 2.5 Cisplatin simulation (CIS model)

The next stage of the dose change simulation we performed with the presence of cisplatin in the target volume. Cisplatin was injected into the target, which was located at a certain depth of water phantom. Cisplatin concentrations were selected on the basis of acceptable doses that were considered in previous works by the authors and higher to evaluate dose changes from cisplatin concentration [23–27], while 0.003 mM is the minimum cisplatin concentration which produces a visible effect in radiobiological experiments after X-ray irradiation. However, chemotherapists do not exceed the recommended daily dose of cisplatin more than 100 mg/m² [28]. Exceeding this dose leads to a sharp probability increase of toxicity in patients, such as ototoxicity, gastrotoxicity, myelosuppression and allergic reactions [29, 30]. It should be noticed, that the cisplatin accumulation in tumor will be lower than injection [31, 32]. An example is the research conducted in-vivo mouse studies [33] in which the authors showed that the highest platinum concentration in a tumor tissue was found at 3 and 4 days after the injection of 25 mg/kg cisplatin, reaching 8.8 µg/mg and 3.8 µg/mg, respectively. A 1–3 mm, 10–13 mm, 30–33 mm and 50–53 mm depths of the target location for X-ray tube simulation and 5–10 mm, 50–55 mm depths of the target location for linac simulation were considered. This allowed us to observe not only the dependence on DEA concentration, but also the dependence on the depth of the target location. The calculations of cisplatin simulation with DEA were carried out while keeping all the parameters of the PDD model concept.

### 3 Results

#### 3.1 Spectrum model

The photon energy spectrum as a function of photon energy for linac is shown in figure 6. The energy spectra of incident photons peak were found at 0.511 MV for the maximum nominal energy of 6 and 10 MV.

The photon beam energy spectra in the tube voltages including 60, 120, 180 and 250 kV by the Geant4 and PClab were calculated. The results are presented in figures 7 to 10.

The results for these energies showed a similar mathematical difference between Geant4 and PClab calculations. Small differences can be associated with different algorithms and cross-section
Figure 6. The estimated X-Ray energy spectra from the target W.

Figure 7. The estimated spectrum for 60 kV X-Ray tube voltage.

Figure 8. The estimated spectrum for 120 kV X-Ray tube voltage.

Figure 9. The estimated spectrum for 180 kV X-Ray tube voltage.

Figure 10. The estimated spectrum for 250 kV X-Ray tube voltage.

files used for different systems. Nevertheless, the results confirmed that the spectrum model is accurate and can be used for dose distribution calculations in water phantom.

3.2 Percentage depth dose model

The PDDs obtained by simulations were compared with experimental data obtained with the linear accelerator Elekta Synergy in Tomsk Regional Oncology Center. The PDDs in figure 11 and 12 are shown for 6 and 10 MV energy photon accordingly. The dose maximum point was determined at 1.5 cm depth for 6 MV and 2.2 cm depth for 10 MV. The theoretical value of the maximum depth of the dose is 1.5 cm for 6 MV and 2.3 cm for 10 MV.
Figure 11. A comparison of PDD curves for a field of $10 \times 10 \text{cm}^2$ from experimental measurements (CC13) and Monte-Carlo calculations for 6 MV linac model.

Figure 12. A comparison of PDD curves for a field of $10 \times 10 \text{cm}^2$ from experimental measurements (CC13) and Monte-Carlo calculations for 10 MV linac model.

Figure 13 shows the deviation of Monte-Carlo calculation from experimental measurements. The mean (maximum) deviation was 0.42% (0.87%) and 0.47% (0.80%) for PClab and Geant4. Figures 14–17 show comparison of PDD obtained from experimental measurements using an ionization chamber and calculated in the Geant4 and PClab. The curves for 60, 120, 180 and 250 kV tube voltage matched very well with experimentally measured PDD values at all depths with the difference of 2% or less. The exception was 1.21 cm depth and 120 kV where the difference of 2.7% at PClab and 3.8% at Geant4 was observed.

3.3 CIS model

The next stage of the dose change simulation we performed in the presence of cisplatin in the target volume at linac and X-ray tube irradiation. The tables 1–5 present the dose-enhancing factor (DEF) for different depth target locations and different cisplatin concentrations calculated by Geant4 and PClab. In each of the simulation cases no DEA (cisplatin) outside the tumor volume was supposed. It’s in order to provide a clear relationship between the DEA concentration and the beam energy.
The dose enhancement factors (eq. (3.1)), defined as the ratio of the dose in the tumor volume (\(D_a\)) with DEA to that dose in the tumor without DEA (\(D\)):

\[
\text{DEF} = \frac{D_a}{D}.
\]  

(3.1)

In case of linear accelerator simulation, 5–10 and 50–55 mm depths of a target location and energy photon beam of 6 MV and 10 MV were considered. This allowed us to observe not only the...
dependence on the agent concentration, but also the dependence on the depth of the target location and the energy of photons. In addition, a linac without a flattening filter (FFF) was considered. The table 1 shows the dose-enhancing factor for reference points at systems with flattening filter and flattening filter free systems (FFF).

As a result, the DEFs calculation for linac does not demonstrate clinically important dose increase. At concentration of 120 mM, dose increase of up to 7.7% ± 3.5% and 3.1% ± 3.5% is observed for 6 MV and 10 MV correspondingly. As well as studies of flattening filter free showed the DEF increase equal to 8.6% ± 3.6% and 8.9% ± 3.6% when irradiated with photon beams of 6 and 10 MV (figure 18).

In the study of the clonogenic survival of breast cancer cells [34], SERs of 1.29 and 1.16 was obtained when irradiated with photon beams energies of 6 and 15 MV. It is interesting that statistically significant SERs were observed in the study [6] when gold nanoparticles with concentration of up to 0.05 mg/ml were introduced into HeLa cell samples and irradiated with a 6 MB linear accelerator without a smoothing photon filter (FFF technology). SER was observed equal to from 1.1 to 1.7. However, mathematical modeling and in-vitro studies on the other hand have shown that antitumor activity is higher when using low-energy photons when comparing the results after irradiation with a megavolt beam of photons [35].

Figure 16. A comparison of PDD between the Monte-Carlo calculations and the experimental measurements for 180 kV X-Ray tube voltage.

Figure 17. A comparison of PDD between the Monte-Carlo calculations and the experimental measurements for 250 kV X-Ray tube voltage.
Table 1. The DEF values for linac in the energy photon beam equal to 6 MV and 10 MV. 6 MV and 10 MV — linac with flattening filter; 6 MV FFF and 10 MV FFF — linac flattening filter free.

| Conc. mM | 6 MV | 10 MV | 6 MV FFF | 10 MV FFF |
|----------|------|-------|----------|----------|
| 5–10 mm  | PC   | G4    | PC       | G4       |
| 12       | 1.0062 | 1.0046 | 1.0000  | 1.0000  |
| 120      | 1.0200 | 1.0768 | 1.0208  | 1.0314  | 1.0327 | 1.0861 | 1.0241 | 1.0830 |
| 50–55 mm | PC   | G4    | PC       | G4       |
| 12       | 1.0000 | 1.0047 | 1.0038  | 1.0000  |
| 120      | 1.0659 | 1.0783 | 1.0102  | 1.0205  | 1.0266 | 1.0858 | 1.0216 | 1.0887 |

(a) 6 MV and 6 MV FFF beams model. (b) 10 MV and 10 MV FFF beams model.

Figure 18. Comparison of DEF from linear accelerator at a cisplatin 120 mM concentration.

In case of the X-ray tube model, the depths of the target location of 1–3 mm, 10–13 mm, 30–33 mm and 50–53 mm and photon beam energy of 60, 120, 180 and 250 kV were considered. Tables 2–5 show the DEF for reference points. Keeping in mind those observations, it can be noted that DEF increases where cisplatin is accumulated. DEF values increase linearly with increasing cisplatin concentration and decrease with increasing depth of the target location. However, the photon energy increase from 60 to 250 kV reduces the effect of PCT due to the decrease of the photoelectric effect cross-section. The highest DEF value is observed when irradiated with 60 kV x-ray.

Figure 19 shows DEF as a function of tumor cisplatin concentration. Based on the orthovoltage X-rays energy considered, the highest degree of dose enhancement occurs for 60 kV and higher DEA concentration. The linearity aspect is in agreement with the result obtained by Solberg et al. [36] (1992) for iodine concentration and research made by Ranjbar et al. (2010) [37] for gold nanoparticles.

Figure 20a presents a comparison between PDD from photon beams with energies of 6 MV, 1.25 MV (Co-60), 60 kV and cisplatin model. Also, figure 20b shows a comparison of the PDD between the 6 MV, 1.25 MV (Co-60), 250 kV and 250 kV with cisplatin.

According to the graph, in the field of DEA accumulation there is a sharp increase in dose not only for surface targets, but also for deeply located targets. For example, Monte-Carlo calculations
Table 2. The DEF for 1–3 mm depth target location.

| Energy, kV | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 |
|------------|-----------|-------|--------|-----------|-------|--------|-----------|-------|--------|-----------|-------|--------|
| 60         | 0.003     | 1.0006| 1.0012 | 1.0000    | 1.0000| 1.0000 | 1.0000    | 1.0000| 1.0000 |
|            | 0.006     | 1.0005| 1.0008 | 1.0000    | 1.0000| 1.0000 | 1.0000    | 1.0000| 1.0000 |
|            | 0.009     | 1.0003| 1.0005 | 1.0020    | 1.0024| 1.0047 | 1.0029    | 1.0029| 1.0030 |
|            | 0.012     | 1.0015| 1.0019 | 1.0025    | 1.0030| 1.0140 | 1.0084    | 1.0074| 1.0014 |
|            | 0.3       | 1.0086| 1.0138 | 1.0121    | 1.0107| 1.0166 | 1.0133    | 1.0068| 1.0052 |
|            | 0.6       | 1.0186| 1.0153 | 1.0130    | 1.0146| 1.0144 | 1.0156    | 1.0044| 1.0047 |
|            | 0.9       | 1.0260| 1.0272 | 1.0233    | 1.0220| 1.0187 | 1.0213    | 1.0092| 1.0130 |
|            | 1.2       | 1.0343| 1.0293 | 1.0252    | 1.0272| 1.0229 | 1.0257    | 1.0012| 1.0013 |
|            | 3         | 1.0851| 1.0842 | 1.0771    | 1.0772| 1.0591 | 1.0587    | 1.0302| 1.0317 |
|            | 6         | 1.1704| 1.1702 | 1.1509    | 1.1510| 1.1033 | 1.1070    | 1.0638| 1.0643 |
|            | 9         | 1.2557| 1.2554 | 1.2238    | 1.2226| 1.1714 | 1.1733    | 1.1172| 1.1124 |
|            | 12        | 1.3396| 1.3268 | 1.2860    | 1.2916| 1.2294 | 1.2278    | 1.1491| 1.1404 |
|            | 30        | 1.8210| 1.8162 | 1.7218    | 1.7394| 1.5489 | 1.5343    | 1.3337| 1.3256 |
|            | 60        | 2.5988| 2.5800 | 2.4155    | 2.4373| 2.0902 | 2.0780    | 1.6522| 1.6665 |
|            | 90        | 3.3372| 3.3146 | 3.1095    | 3.1361| 2.6980 | 2.6644    | 1.9760| 1.9834 |
|            | 120       | 4.0348| 4.0013 | 3.8555    | 3.9135| 3.1744 | 3.1220    | 2.2702| 2.2866 |

Table 3. The DEF for 10–13 mm depth target location.

| Energy, kV | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 | Conc., mM | PClab | Geant4 |
|------------|-----------|-------|--------|-----------|-------|--------|-----------|-------|--------|-----------|-------|--------|
| 60         | 0.003     | 1.0012| 1.0001 | 1.0000    | 1.0000| 1.0000 | 1.0000    | 1.0000| 1.0000 |
|            | 0.006     | 1.0000| 1.0001 | 1.0001    | 1.0000| 1.0000 | 1.0000    | 1.0000| 1.0000 |
|            | 0.009     | 1.0007| 1.0014 | 1.044     | 1.0000| 1.0011 | 1.0000    | 1.0000| 1.0000 |
|            | 0.012     | 1.0000| 1.0000 | 1.0875    | 1.0000| 1.0012 | 1.0009    | 1.0000| 1.0000 |
|            | 0.3       | 1.0148| 1.0099 | 1.0090    | 1.0092| 1.0111 | 1.0183    | 1.0035| 1.0035 |
|            | 0.6       | 1.0176| 1.0169 | 1.0161    | 1.0150| 1.0097 | 1.0246    | 1.0084| 1.0072 |
|            | 0.9       | 1.0293| 1.0250 | 1.0270    | 1.0244| 1.0211 | 1.0314    | 1.0175| 1.0164 |
|            | 1.2       | 1.0305| 1.0336 | 1.0287    | 1.0307| 1.0144 | 1.0323    | 1.0126| 1.0138 |
|            | 3         | 1.0842| 1.0860 | 1.0738    | 1.0717| 1.0565 | 1.0610    | 1.0365| 1.03512 |
|            | 6         | 1.1739| 1.1728 | 1.1519    | 1.1493| 1.1126 | 1.1216    | 1.0557| 1.0568 |
|            | 9         | 1.2611| 1.2588 | 1.2247    | 1.2237| 1.1753 | 1.1798    | 1.0998| 1.0986 |
|            | 12        | 1.3348| 1.3438 | 1.2869    | 1.2973| 1.2165 | 1.2372    | 1.1410| 1.1407 |
|            | 30        | 1.8477| 1.8555 | 1.7324    | 1.7385| 1.5681 | 1.5684    | 1.3198| 1.3189 |
|            | 60        | 2.6661| 2.6910 | 2.4120    | 2.4321| 2.1225 | 2.1228    | 1.6669| 1.6670 |
|            | 90        | 3.48042| 3.5167 | 3.1560    | 3.1822| 2.6846 | 2.6771    | 2.0013| 2.0014 |
|            | 120       | 4.2669| 4.3215 | 3.8518    | 3.8963| 3.2374 | 3.2360    | 2.3130| 2.3159 |
Table 4. The DEF for 30–33 mm depth target location.

| Energy, kV | Conc., mM | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 |
|-----------|-----------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|
| 60        | 0.003     | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.006     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.009     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.012     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.3       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.6       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.9       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 1.2       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 3         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 6         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 9         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 12        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 30        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 60        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 90        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 120       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |

Table 5. The DEF for 50–53 mm depth target location.

| Energy, kV | Conc., mM | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 | PClab | Geant4 |
|-----------|-----------|-------|--------|-------|--------|-------|--------|-------|--------|-------|--------|
| 60        | 0.003     | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.006     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.009     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.012     | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.3       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.6       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 0.9       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 1.2       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 3         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 6         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 9         | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 12        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 30        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 60        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 90        | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
| 120       | 1.0000    | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 | 1.0000| 1.0000 |       |        |
Figure 19. The dependence of DEF on cisplatin concentration at X-ray energies of 60kV to 250kV.

(a) 60kV, 6MV, Co-60 and simulation of cisplatin in target.
(b) 250kV, 6MV, Co-60 and simulation of cisplatin in target.

Figure 20. A comparison of PDD in water between photon beam models and simulation of cisplatin in target.

show that the presence of cisplatin in the target contributes to the high dose increase even at 5 cm depth of target location.

4 Conclusion

This research considers potential dose increase in a target due to cisplatin (Pt) concentration and radiation type. Although, we got results for high concentrations of cisplatin, which has not been clinically tested for concentrations above 30 mM. In general, Monte-Carlo results showed that the dose escalation in a target at orthovoltage x-ray and megavolt photon beams can be due to photon-capture therapy. For X-rays photon beams the DEF was higher than for a megavoltage photon beam generated from linear acceleration. For 60kV x-rays, a tremendous DEF was seen, in the range of almost $4.3 \pm 0.17$ at the highest Pt concentration (120 mM). The DEF indicates become less while energy increases up to 250 kV. These differences become important with very high DEA concentrations, up to 120 mM in tumor.

We should also notice that the DEF is higher in linacs without flattening filter than in linacs with flattening filter. For 6 and 10 MV photon beams with flattening filter the DEF up to 1.077 and
1.031 was seen. As well as 6 and 10 MV without flattening filter gives DEF equal to 1.086 and 1.089. It can be assumed that this phenomenon is due to the fact that the flattening filter system absorbs low-energy photon beam. At the same time these low-energy photons cause a photoelectric effect in FFF systems and a corresponding dose increase in the target is observed. Perhaps from the point of view of clinical significance the DEF values obtained for the 6 and 10 MV are not important. However, from the point of view of considering the error of dose adjustment these factors can be taken into account, for example, with simultaneous chemoradiation treatment or the other DEA introduction (6 MV–7.7% ± 3.5%; 6 MV FFF–8.6% ± 3.6%; 10 MV–3.1% ± 3.4%; 10 MV FFF–8.9% ± 3.3%; at a concentration of cisplatin 120 mM in the target).

In this way, Monte-Carlo simulation showed that the dose-enhancing factor increases with higher values of cisplatin concentrations and lower photon energy. The result of this study may be useful in planning cisplatin-based chemoradiotherapy and may improve the efficacy of tumor therapy application.

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