On the influence of chemotherapy on the Bragg peak parameters in the water cube model

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Results of the study of influence of the variability of chemical composition of tissues on characteristics of Bragg peak are presented. Few approaches to modelling of the variability of chemical composition are proposed. The obtained numerical results allow to estimate how chemotherapy affects the Bragg peak characteristics.

1. Chemotherapy

Kinds of chemotherapy:

- systemic chemotherapy — drug is disposed by intravenous injection, intramuscularly, hypodermicaly etc.;
- regional chemotherapy — drug is injected into blood vessel feeding tumor by means of infusion or perfusion;
- local chemotherapy — injection of drug in visceral cavities, intrathecally or locally (externally).

1.1. Estimate of drug concentration for intravenous injection

List of drugs and maximum doses for intravenous injection are given in the table 1.

If the drug may be used to treat few kinds of cancer those case is choosed in our study where required concentration is greater. Dose is given in milligrams per square meter of the human body surface area (BSA). BSA is less dependent on excess of adipose tissue so it well characterizes metabolic exchange.

Following methods of BSA calculation were considered:

- DuBois and DuBois formula [13]: BSA $= 0.007184 H^{0.725} W^{0.425}$
- Mosteller formula [14]: BSA $= \sqrt{\frac{HW}{3600}}$.
- Haycock formula [15]: BSA $= 0.024265 H^{0.3964} W^{0.5378}$

Table 1. Maximum dose of intravenous injection[12].

Drug	Dose, mg/m^2
Carboplatin	360
Epirubicin	100-120
Cisplatin	75-100
Cyclophosphamide	600
Vinblastine	1.4
Vincristine	18.5

Here H is a person's height in centimeters and W is weight in kilograms. In our simulations the Mosteller formula was used. Data from [18] for medium age were taken: 177 cm, 80 kg for men and 164 cm and 65 kg for women, so we obtain BSA: 1.98 m^2 for men and 1.72 m^2 for women. Estimates for maximum concentration of drugs are:

- Fluorouracil: $(1000\ mg/m^2 * 1.72\ m^2)/65\ kg = 26.46\ mg/kg$;
- Gemcitabine: $(1250\ mg/m^2 * 1.98\ m^2)/80\ kg = 30.94\ mg/kg$ for men.

Commonly used concentrations of other drugs are much less. Hence if a drug is uniformly distributed over the body volume by blood flow its concentration is too small to affect the dose-depth distribution.

1.2. Estimation of drug concentration in regional chemotherapy

Main goal of the regional chemotherapy is injection of significant doses of drugs (few orders of magnitude greater than doses for intravenous injection) without excessive harm to other organs. Isolated perfusion is realized surgically. Region of the human body which should be treated is isolated and exposed to high concentrated drug by means of external pump. To eliminate excessive drugs in greater circulation, at the end of isolated perfusion chemofiltration is used. Hence drugs in regional chemotherapy, most probably doesn't affect significantly the depth-dose distribution in radiotherapy.

1.3. Estimation of drug concentration in local chemotherapy

In local chemotherapy drug absorption is slower so drug is concentrated in small volume. It means that if local chemotherapy should be used in combined treatment procedure influence of drugs on depth-dose distribution must be estimated and possibly taken into account. List of some drugs and maximum doses for local chemotherapy is given in the table 2.

2. Numerical simulation

For the sake of computer simulations we considered the target which is cube with sizes $10 \times 10 \times 10$ cm. Medium filling the target volume is pure water or water solution of the

Table 2. Chemical composition and maximum dose for local chemotherapy. [17]

Drug	Chemical composition	Dose, mg
Bleomycin	$C_{55}H_{85}N_{17}O_{21}S_3$	10-20 mg intramuscularly or subcutaneously
Cytarabine	$C_9H_{13}N_3O_5$	20 mg subcutaneously
Mitomycin	$C_{15}H_{18}N_4O_5$	40 mg into the cavity of the bladder
Thiotepa	$C_6H_{12}N_3PS$	30-60 mg into the cavity of the bladder

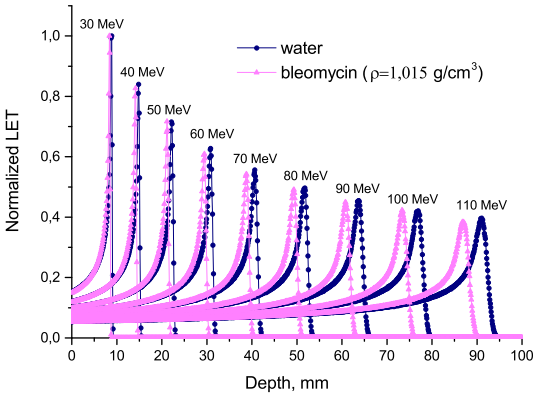

Figure 1. Normalized LET profile for pure water and water solution of bleomycin for proton beam

drug from the above given list of five drugs. Let us consider bleomycin. For a given mass of water for injection its mass fraction (0.985) and mass fraction of the drug (0.015) are obtained. Then atoms of chemical elements are added proportionally to the number of atoms in the molecule. In the case of other liquid as a solution base it should be defined in the same way.

For the bleomycin solution in computer simulations with Geant4 we used following parameters:

- $\rho = 1.015\ g/cm^3$;
- fraction $= 0.015$.

Chemical composition of drug solutions for injections is taken from [16].

Linear Energy Transfer (LET) distributions were calculated. LET describes interaction between radiation and matter and is defined as follows:

$$LET = \frac{\delta E}{\delta x}$$

where δE is the energy loss of charged particles on the distance δx.

Simulation results for water and bleomycin, mitomycin, tyotepa, cisplatin are given in figs. 1-2. Sampling size corresponds to 10^4 protons passed through medium.

It is seen that presence of drugs in the volume under consideration affects the Bragg peak position. Difference between peaks in pure water and in the drug solution

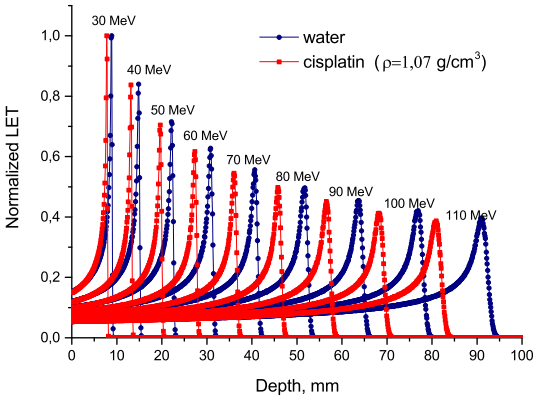

Figure 2. Normalized LET profile for pure water and water solution of cisplatin for proton beam

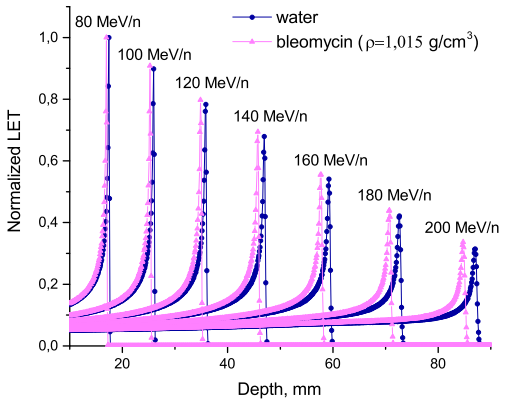

Figure 3. Normalized LET profile for pure water and water solution of bleomycin for carbon ion beam

is observed even for small amount of drugs. Difference of peaks positions in pure water target and in the drug solution increases with increasing of protons penetration depth and the beam energy. Change of the Bragg peak position is maximum for thiotepa and cisplatin. Their solutions have maximum densities. We also observed that shift of the Bragg peak position depends not only on the solution density but also on its chemical composition, and more precisely, on fraction of heavier elements. For example, despite difference of density, shift of the Bragg peak is nearly the same for solutions of thiotepa and mitomycin. It may be seen also that in presence of drug the Bragg peak is shifted toward the front target surface. As to the maximum energy it is nearly the same.

Normalized LET profiles for the same set of drugs but for carbon beam are presented in figs. 3-4. It may be seen that depth of the Bragg peak localization is less for the same energy of the carbon ion beam and it's shift due to drug admixture is smaller than in the case of the proton beam.

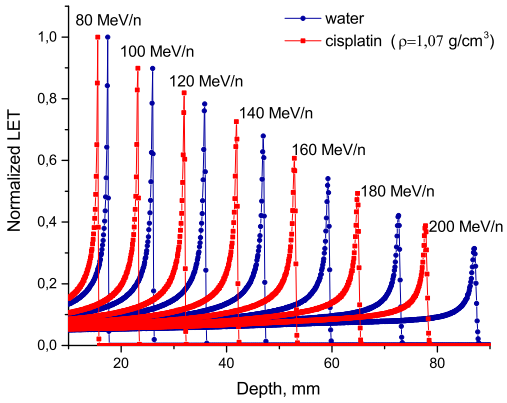

Figure 4. Normalized LET profile for pure water and water solution of cisplatin for carbon ion beam

3. Conclusion

We proposed computational models which may be used to estimate influence of variations of chemical composition of internal organs caused by chemotherapy on efficiency of radiation therapy. Computer simulations were performed with software package Geant4 for set of medicals and two kinds of radiotherapeutic beams: proton and carbon ion. Range of beam energies corresponds to the ones used in the hadron therapy. Cubic target was considered with medicine water solution. Concentrations were derived from most widely used methods of chemotherapy. Results of numerical simulations show that depth-dose profile is affected not only by therapeutic beam but also by variations of chemical composition caused by chemotherapy in combined methods of cancer treatment. Such effect have to be taken into account in any particular case. To arrive at more accurate conclusions more detailed computations with more realistic models should be performed.

4. References

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