FEASIBILITY OF USING 6 MV PHOTON BEAMS IN CONTRAST-ENHANCED RADIOTHERAPY

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Contrast-enhanced radiotherapy (CERT) is a type of radiation therapy used to enhance the radiation dose absorbed by the tumor while sparing surrounding healthy tissues. The present study aims to assess feasibility of using 6 MV photons to increase radiation absorption in CERT. The dose absorbed by iodinated water was directly measured by ferrosulphate dosimetry. Concentrations of iodine (a dose-enhancing agent) ranged from 2.5 to 50 mg/ml. Solutions were exposed to 5 Gy radiation generated by the clinical linear accelerator SL75-5MT (Russia). The radiation dose applied did not account for increased absorbance due to the presence of iodine atoms. No reliable increase in the absorbed dose was observed for iodine concentrations ranging from 2.5 to 20 mg/ml. For 50 mg/ml concentrations the absorbed dose increased by 13% ± 5 % ($p < 0.05$). Normally, dose-enhancing concentrations observed in CERT studies range from 2.5 to 15 mg/ml, therefore, as demonstrated by our findings, employing 6 MV photon energy spectra in order to reach a therapeutically significant effect is unreasonable.

Keywords: contrast-enhanced radiotherapy, ferrosulphate dosimetry, megavolts radiation, dose enhancement factor

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Received: 25.08.2017 **Accepted:** 30.08.2017

ВОЗМОЖНОСТЬ ПРОВЕДЕНИЯ ФОТОН-ЗАХВАТНОЙ ТЕРАПИИ С ИСПОЛЬЗОВАНИЕМ 6 МВ ФОТОННОГО ИЗЛУЧЕНИЯ

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Фотон-захватная терапия (ФЗТ) — метод лучевой терапии, который обеспечивает повышение поглощенной дозы в опухоли без дополнительной лучевой нагрузки на окружающие нормальные ткани. В работе представлены результаты экспериментального исследования возможности увеличения поглощенной дозы при ФЗТ за счет использования 6 МВ фотонного излучения. При помощи водных растворов ферросульфатных дозиметров было проведено прямое измерение величины поглощенной дозы в воде, содержащей йод (дозоповышающий агент) в концентрации от 2,5 до 50 мг/мл. Облучение растворов проводили на линейном медицинском терапевтическом ускорителе СЛ75-5-МТ (Россия) в дозе 5 Гр без учета возможного увеличения поглощенной дозы за счет присутствия атомов йода. Для концентраций йода 2,5–20 мг/мл достоверного увеличения поглощенной дозы зарегистрировано не было. Для концентрации йода 50 мг/мл увеличение поглощенной дозы составило 13 ± 5 % ($p < 0,05$). Поскольку типичные концентрации дозоповышающих агентов при введении в организм пациентов, как правило, находятся в диапазоне 2,5–15 мг/мл, использование 6 МВ фотонного излучения для достижения терапевтически значимого противоопухолевого эффекта не представляется целесообразным.

Ключевые слова: фотон-захватная терапия, ферросульфатная дозиметрия, мегавольтное излучение, фактор повышения дозы

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Статья получена: 25.08.2017 **Статья принята к печати:** 30.08.2017

Contrast-enhanced radiotherapy (CERT) is a new binary treatment modality that advantageously ensures enhancement of the radiation dose absorbed by a tumor while sparing surrounding healthy tissues. This effect is achieved by using special drugs that contain dose-enhancing agents (DEAs), i. e. chemical elements with $Z > 52$ (I, Gd, Au, B, etc.) and thus have a better absorption capacity than constituents of soft biological tissues.

Fig. 1 shows mass energy absorption coefficients μen for a number of chemical elements plotted against photon energy. As demonstrated by the graph, elements with different Z have considerably different absorption capacity only when exposed to ionizing photons with an energy spectrum between 30 and 300–500 keV [1] characteristic of orthovoltage X-rays. Most studies on CERT employ sources of ionizing radiation that emit in this particular spectrum [2–7].

Clearly, the difference is negligible in the absorption capacity of DEAs and soft tissues exposed to >500 keV photon energies. However, a number of authors report an increased therapeutic effect following contrast-enhanced radiation treatment with megavoltage X-rays (>6 MV) [8–13]. In their experiments, dose enhancement was attempted by the use of gold nanoparticles, platinum compounds and gadolinium-containing nanostructures. Possible mechanisms of enhanced absorption were also suggested [14–16]. It was hypothesized that as primary radiation scatters in a DEA-loaded tumor, the latter accumulates the sufficient amount of low-energy photons capable of interacting with the DEA. As orthovoltage X-rays interact with the DEA, the environment surrounding the DEA atom gets ionized just a few nanometers away from it. Ionization generates a large number of radical ions capable of affecting biological structures from a longer distance (up to several mm away from the atom).

Other researchers attempted to estimate an increase in the absorbed radiation dose using polymer gel dosimeters and EPR dosimeters (EPR stands for electron paramagnetic resonance) loaded with DEAs and irradiated with 6 MV photons. In the work [17] 18 mg/ml gold concentrations were introduced into polymer gel dosimeters, but no reliable dose enhancement was registered. In the experiments with the alanine EPR-dosimeter containing 30 mg/ml gold [18] dose enhancement was 10 %.

This brings up the question: is the therapeutic effect of 6 MV CERT due to the mere physical increase in the absorbed dose or to the sensitizing effect of radiation on tumor cells? We decided to find out how the absorbed radiation dose increases in iodinated water irradiated with 6 MV photons. Unlike other researchers who used polymer gel and alanine EPR dosimeters in which radical ions may not be so mobile as in water, we used aqueous solutions for our measurements because in water radical ions can travel unobstructed by large molecules and, therefore, can be registered more effectively.

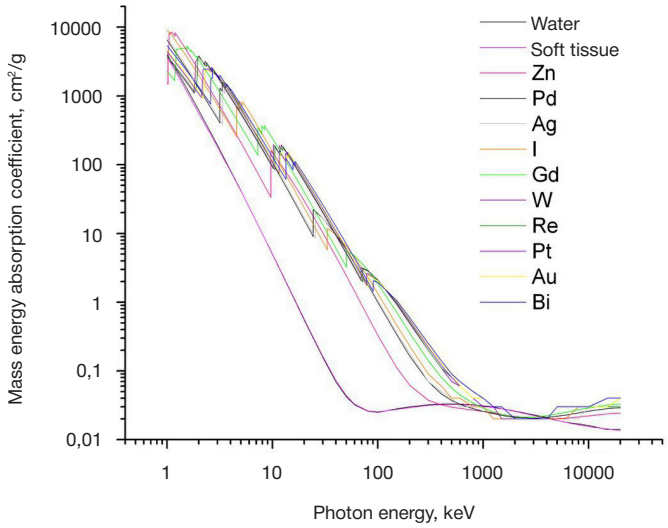

Fig. 1. Dependence of mass energy absorption coefficient on incident photon energy

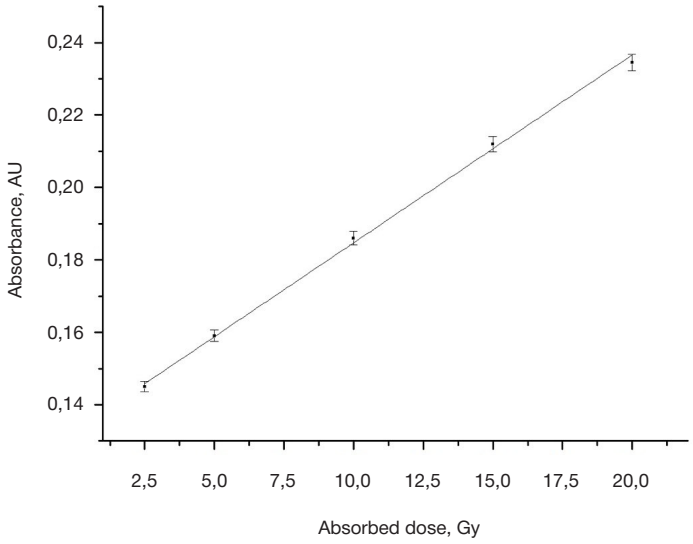

Fig. 2. The graph shows dependence of absorbance of the ferrous sulphate dosimeter on the absorbed radiation dose

METHODS

To measure dose enhancement in aqueous iodinated solutions, we resorted to ferrous sulphate dosimetry. The main problem of absorbed dose quantification in the presence of DEAs is the short range of secondary radiation (from a few nanometers for Auger electrons to a few micrometers for photoelectrons and characteristic X-rays), which imposes certain limitations on the use of conventional dosimetry techniques. Here, liquid ferrous sulphate dosimetry offers a solution. This technique employs oxidation of Fe^{2+} to Fe^{3+} by highly reactive products of water radiolysis induced by ionizing radiation. The number of yielded Fe^{3+} ions depends on the absorbed radiation dose and therefore allows to calculate the exact value of the latter. The dosimeter solution can be "supplemented" with DEA; thus Fe^{3+} ions will be in close proximity to DEA atoms, and the effect of secondary radiation on the total absorbed dose can be estimated.

In our experiment dose enhancement was attempted with iodine (Ultravist 370, a iodine-based contrasting agent by Bayer, Germany), whose atomic number is 53. Iodine concentrations of 2.5, 5, 10, 20 and 50 mg/ml were created in the solutions of ferrous sulphate dosimeters. The solutions were prepared as described in [19].

Spectrophotometric measurements of absorbance at the peak of light absorption by Fe^{3+} ions are performed at 303 nm wavelength. The optical absorption spectrum of iopromide interferes with that of iron; therefore, we modified the dosimeter by adding ammonium rhodanide (thiocyanate) NH_4SCN. Once ferric ions reacted with rhodanide, a intensely colored orangish-red Fe^{3+}/ thiocyanate complex was formed with the absorption peak at 460 nm. We added 100 µl of 0.1 g/ml ammonium rhodanide solution to every irradiated iodinated dosimeter solution and then measured the absorption spectrum and absorbance for the Fe^{3+}/thiocyanate complex using Cary 50 spectrophotometer (Varian Australia Pty, Australia).

An increase in the absorbed dose can be expressed using a dose enhancement factor (DEF): $DEF = D_{contrast}/D$, where $D_{contrast}$ is the dose absorbed by the irradiated dosimeter containing a dose-enhancing agent, as measured by spectrophotometry, and D is the absorbed dose in the absence of DEA. The absorbed dose was calculated based on the calibration curve for doses ranging from 2.5 to 20 Gy.

In our experiment we used the 6 MV clinical electron accelerator SL75-5-MT (Efremov Research Institute of Electrophysical Equipment, Russia) from the radiation therapy unit of Blokhin Russian Cancer Research Center. The accelerator generates bremsstrahlung radiation with photon energies up to 6 MeV. Prior to irradiation, the dosimeter solutions were placed in 40 mm Petri dishes, 2.5 ml of solution per dish. Irradiation time was 100 seconds, which is sufficient for iodine-free water to absorb 5 Gy. No tissue equivalent scatterers were used in this study, because its aim was to model conditions for surface irradiation, typical for in vitro and *in vivo* studies (in mice and rats with transplanted tumors).

Spectrophotometric measurements were done in 6 repeats for each DEA concentration. The mean absorbed dose and the standard error of the mean were calculated for each concentration considering Student's coefficient. Statistical significance was estimated by the Mann–Whitney U-test.

RESULTS

The calibration curve in Fig. 2 shows that absorbance of the ferrous sulphate dosimeter is linearly dependent on the absorbed dose (doses range from 2.5 to 20 Gy).

Mean values of the dose enhancement factor for each studied iodine concentration are shown in the Table. A 13 % dose enhancement was observed at a concentration of 50 mg/ml. For other studied concentrations DEF was <1.

DISCUSSION

The obtained results show that typical concentrations of DEA accumulated in the tumor (2–50 mg/ml) do not have any clinically significant effect on the radiation dose absorbed during CERT with 6 MV photons. Absorbed dose enhancement does not exceed the uncertainty value at iodine concentrations ≤20 mg/ml. Significant dose enhancement (by 13 ± 5 %) was observed at a 50 mg/ml iodine concentration. The results of our study are consistent with the findings of other authors [17, 18]. It should be noted that iodine concentrations >20 mg/ml can be reached only by direct injections of DEA into the tumor, which is strongly disapproved of by the medical community. Systemically administered DEAs usually have iodine concentrations ranging between 2 and 15 mg/ml [2, 20]. To sum up, no clinically significant dose enhancement was registered in the solutions irradiated with 6 MV photons at typically used iodine concentrations, which means that no improved therapeutic effect should be expected.

CONCLUSIONS

Our findings suggest that standard sources of 6 MV energies used in clinical routine cannot ensure clinically significant enhancement of the absorbed dose for contrast-enhanced radiotherapy. The antitumor effect of 6 MV photons in the presence of dose-enhancing agents in the tumor is likely to be a case of radiosensitization and is not caused by increased absorption of radiation by the tumor. A question remains whether the use of flattening filters for orthovoltage and kilovoltage energies can be avoided during 6 MV CERT.

Values of dose enhancement factor measured at different iodine concentrations

Iodine concentration, mg/ml	DEF
2.50 ± 0.08	1.00 ± 0.05
5.0 ± 0.1	0.90 ± 0.08
10.0 ± 0.3	1.00 ± 0.05
20.0 ± 0.6	1.00 ± 0.05
50.0 ± 1.5	1.13 ± 0.05*

Note. * — difference is statistically significant ($p < 0.05$).

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