IODINE QUANTIFICATION WITH COMPUTED TOMOGRAPHY FOR THE PURPOSE OF DOSE ASSESSMENT IN CONTRAST ENHANCED RADIOTHERAPY

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In vivo quantitative determination of high-Z elements such as iodine gadolinium, gold, etc. is an important issue for contrast enhanced radiotherapy (CERT) that aggravates its clinical implementation. X-ray computed tomography (CT) could be a reliable, convenient and universal method for this task. The aim of this study was to demonstrate the feasibility of iodine quantification with CT in a tissue equivalent phantom, meeting the demands for CERT. The results show a linear relationship between iodine concentration and radiopacity on tomographic images expressed in Hounsfield units (HU) over an iodine concentration range of 0.5–50 mg/ml. Furthermore, iodine quantification with CT proofed to be suitable for CERT since the deviation between CT-derived and actual iodine concentration does not exceed 5 % in the concentration range of 10–50 mg/ml. More significant deviations were observed for concentrations below 5 mg/ml with up to 80 %, which is still acceptable for CERT since the corresponding error for the absorbed dose in that range is less than 2.8 %. X-ray beam hardening within the tissue equivalent object does not significantly influence the accuracy of iodine quantification. The placement of iodine water solutions at the surface or in the centre of a visualized object during iodine quantification leads to a less than 2 % change in the determined iodine concentration.

Keywords: contrast enhanced radiotherapy, computed tomography, iodine, quantification, dosimetry

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КОЛИЧЕСТВЕННОЕ ОПРЕДЕЛЕНИЕ ЙОДА ПРИ ПОМОЩИ РЕНТГЕНОВСКОЙ КОМПЬЮТЕРНОЙ ТОМОГРАФИИ ДЛЯ ДОЗИМЕТРИЧЕСКОГО ОБЕСПЕЧЕНИЯ ФОТОН-ЗАХВАТНОЙ ТЕРАПИИ

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Количественное определение *in vivo* дозоповышающих агентов, то есть элементов с Z >52, при фотон-захватной терапии (ФЗТ) необходимо для внедрения метода в клиническую практику. Проведено исследование возможности количественного определения йода (Z = 53) в тканеэквивалентном объекте (полиэтиленовом фантоме) при помощи рентгеновской компьютерной томографии (КТ). Показано, что зависимость значений рентгеноплотности водных растворов йода на томограммах фантома от концентрации йода носит линейный характер в диапазоне концентраций йода от 0,5 до 50 мг/мл. Характеристики предлагаемого метода количественного определения йода при помощи КТ соответствуют потребностям ФЗТ. Отклонение измеренного по томограммам содержания йода в растворах от их истинных значений не превышает 5 % в диапазоне концентраций йода от 10 до 50 мг/мл. Для растворов с концентрацией йода менее 5 мг/мл отклонение достигает 80 %. Однако и этот результат является приемлемым для ФЗТ, так как для концентраций йода менее 5 мг/мл неопределенность величиной в 80 % в измерении концентрации йода приводит к неопределенности определения величины поглощенной дозы не более чем в 2,8 %. Изменение спектра рентгеновского излучения в тканеэквивалентом объекте не оказывает существенного влияния на характеристики предлагаемого метода. Сравнение градуировочных кривых, построенных для растворов, расположенных около поверхности объекта и в его глубине, показало, что разница между определяемыми по ним значениями концентрации йода не превышает 2 %.

Ключевые слова: фотон-захватная терапия, компьютерная томография, йод, количественное определение, дозиметрия

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Effectiveness and clinical potential of contrast enhanced radiation therapy (CERT) in treating malignant tumors, in particular brain tumors, have been demonstrated by many Russian and foreign researchers [1–5]. CERT relies on the absorption of orthovoltage X-rays in the range of 30–300 keV by high-Z elements introduced into the tumor. This method ensures enhancement of the absorbed radiation dose. X-ray absorption is better in high-Z elements, with Z >52 (for the sake of convenience, they will be further referred to as dose enhancers, DE) than in H, C, O, N, or other elements that constitute soft biological tissues [6].

Phase I clinical trials of CERT-based treatment of brain tumors using a modified CT (computed tomography) scanner were first conducted in the USA in the 1990s [2]. Currently, similar studies are carried out in France at the European Synchrotron Radiation Facility [7]. Though they have already yielded some encouraging results, CERT may still be unable to move on to a further research stage: an accurate method for quantification of DE distribution in tumors and surrounding tissues before and after irradiation has not been developed yet. In CERT, the absorbed radiation dose depends on the DE concentration in the target object and can increase 1.5–5 times compared to the dose absorbed by the same object that was not preloaded with DE [8–12]. Therefore, it would be impossible to elaborate a suitable radiation scheme and control a radiation dose delivered to and absorbed by patient's tissues, which is critical for further clinical research, without developing a method for DE quantification in malignant and healthy tissues.

In the studies mentioned above, radiation schemes did not take into account the presence of DE in the target object. Irradiation mode and duration were chosen based on the interaction of X-rays with soft tissues; the energy released from DE atoms was disregarded. Therefore, radiation was delivered in fractionated doses, similar to conventional external beam radiotherapy. The DE-related enhancement of the absorbed dose was analyzed later when study results were processed and data from CT scans performed in the preparatory stage of the research were averaged over all patients. In calculations of the absorbed doses, DE distribution in tumors was perforce considered uniform. No criteria were proposed to estimate DE content in the target object, and their impact on the total radiation dose absorbed by the tumor was not therefore considered. Obviously, accurate quantification of high-Z elements in patient tissues *in vivo* is essential for effective and safe CERT-based treatment of malignant tumors.

CT seems to be the most appropriate method for DE quantification in CERT. CT and CERT rely on the same physical principle, i. e. absorption of X-rays by a substance. CT is widely used in clinical routine and is one of the major medical imaging techniques. The feasibility of CT-based DE quantification is underpinned by the basic physics of CT and has been experimentally proved by a number of researchers [13–15]. However, the accuracy of DE quantification by CT still remains unclear.

The aim of this work was to demonstrate the feasibility of CT-based iodine determination in a tissue equivalent phantom and to assess the accuracy of this method and the effect that X-ray voltage and non-uniform attenuation of various components of X-ray energy spectrum occurring in the deep layers of the phantom have on it.

METHODS

For this study, we fabricated a polyethylene phantom sized 134 × 134 × 63 mm. We made two perpendicular rows of holes in it (superficial and going through deeper layers) to place several 250 µl microtubes filled with aqueous iodine solutions with iodine concentrations ranging from 0.5 to 50 mg/ml (Fig. 1). We used iopromide (marketed as Ultravist 370) by Bayer Schering Pharma AG, Germany. To prepare aqueous iodine solutions, Ultravist 370 that originally contained 370 mg/ml iodine was diluted down using automatic pipette. The phantom with microtubes in it was scanned with the Siemens Biograph 40 CT scanner (Siemens, Germany) operated at different X-ray tube voltages of 80, 100, 120 and 140 kV and 200 mA current. Images were reconstructed using a standard B30f kernel. Quantitative analysis of DICOM images was performed using the ImageJ software (National Institutes of Health, USA). The same software was used to calculate mean radiopacity of iodine solutions expressed in Hounsfield units (HU) and standard deviations. Linear approximation of the obtained mean values was performed using the R environment (R Foundation).

RESULTS

Fig. 2 shows a relationship between radiopacity of aqueous iodine solutions and their iodine concentrations. It was linear (R2 = 0.998) at all studied concentrations ranging from 0.5 to 50 mg/ml. Using the obtained data, calibration curves were constructed. Deviations between iodine concentrations calculated from the calibration curves and their actual values are shown in the table below. They did not exceed 5 % for concentrations between 10 and 50 mg/ml. For a 5 mg/ ml concentration, the deviation was 5–10 %. The biggest deviation (up to 80 %) was observed in solutions with iodine concentrations below 1 mg/ml. A slight change in radiopacity was observed related to the location of the microtube. On the graph, the calibration curves for the solutions placed closer to the phantom's surface appeared below the calibration curves constructed for the solutions placed deeper inside the phantom. However, the difference between the expected concentrations of the solution and the concentrations calculated from the calibration curves did not exceed 2 % at all operating voltages.

DISCUSSION

We have conducted a pioneer study of DE quantification using a CT scanner and assessed the accuracy of the proposed method considering the challenges faced by contrast enhanced radiation therapy. The effect of varying operating X-ray tube

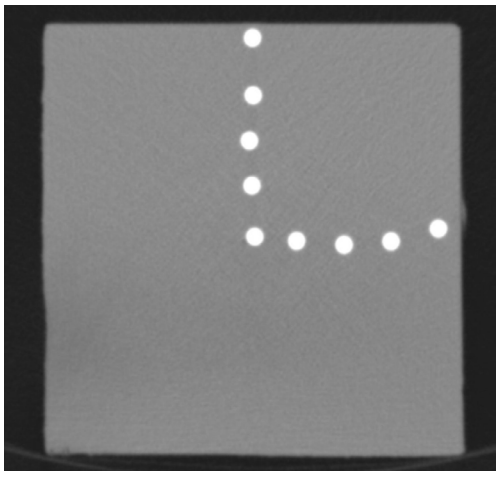

Fig. 1. A CT image of a polyethylene phantom with microtubes in it containing a 35 mg/ml aqueous iodine solution. Operating voltage is 80 kV

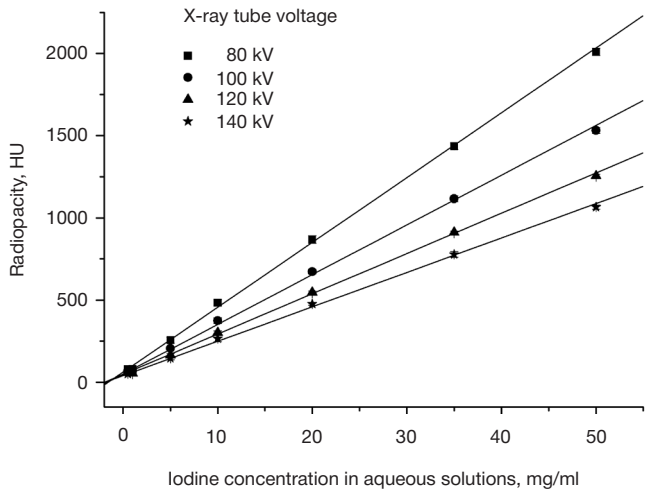

Fig. 2. Calibration curves showing the relationship between radiopacity (expressed in Hounsfield units, HU) and iodine concentrations at X-ray tube voltages of 80, 100, 120 and 140 kV for solutions placed inside the phantom

voltages on the radiopacity of aqueous iodine solutions was studied in a tissue equivalent phantom. We also investigated the relationship between the radiopacity of solutions and the location of the microtubes containing the former (closer to the phantom's surface or in its center). The relationship between radiopacity of aqueous iodine solutions and their iodine concentrations was linear for concentrations ranging from 0.5 to 50 mg/ml at all applied voltages. As we expected, the method exhibited higher sensitivity at 80 kV comparing to 100, 120 and 140 kV voltages. However, this difference in sensitivity is not critical for CERT and does not affect the accuracy of CT-based DE quantification (see the table below); the latter is more influenced by varying HU in the studied area. Thus, the choice of the optimal voltage for DE quantification can be based on other more important criteria [6, 16].

In spite of the considerable deviation between the calculated iodine concentrations and their actual values over the range of 0.5 to 5 mg/ml (up to 80 %), it is acceptable for CERT planning and absorbed dose calculation. As shown previously [16], the increase in the absorbed dose in CERT depends on DE concentration and this relationship can be described linearly (R2 = 0.99764). Thus for the calculation of the absorbed dose, the absolute error of DE quantification is important, and its percentage value is negligible. The observed 80 % uncertainty for a concentration of 1 mg/ml corresponds to the absolute error of 0.8 mg/ml, which in turn leads to a less than 2.8 % change in the absorbed dose value, which is seen as acceptable in radiation therapy.

Thus, the proposed method for CT-based iodine quantification allows the use of the quantitative data on DE distribution for CERT planning and dose control. The accuracy of CT-based DE quantification can be improved by developing special algorithms of image reconstruction aimed to obtain images with lower contrast and sharpness and less varying HU for a homogeneous radiopaque object. Beam hardening in the studied object does not significantly change the accuracy of iodine quantification. CT-based iodine quantification of DE *in vivo* renders it possible to place the reference samples close to a patient and does not require an anthropomorphic phantom for calibration.

CONCLUSIONS

We have experimentally proved the feasibility of CT-based iodine quantification in the tissue equivalent phantom. The method proved to be rather reliable and can be applied for dose assessment and CERT planning. The method is stable in the wide range of X-ray tube voltages and DE concentrations and can be used to study variously shaped objects of different length. CT is also a universal method for DE quantification.

Iodine concentrations in aqueous solutions measured by a CT scanner and their deviations from actual values at various voltages

Actual value of iodine concentrations in aqueous solutions, mg/ml	X-ray tube voltage							
	80 kV		100 kV		120 kV		140 kV	
	Iodine concentration in aqueous solutions (mg/ml) measured by CT and its deviation from the actual value (%)							
	mg/ml	%	mg/ml	%	mg/ml	%	mg/ml	%
0.50 ± 0.01	0.11 ± 0.08	77.1	0.18 ± 0.13	63.3	0.28 ± 0.2	43.9	0.13 ± 0.09	74.8
1.00 ± 0.02	0.18 ± 0.07	81.9	0.39 ± 0.16	60.8	0.10 ± 0.15	89.8	0.63 ± 0.25	37.5
5.0 ± 0.1	4.7 ± 0.2	7.1	4.80 ± 0.2	3.8	4.7 ± 0.2	6.9	4.7 ± 0.2	5.5
10.0 ± 0.2	10.50 ± 0.2	5.0	10.5 ± 0.2	4.7	10.3 ± 0.2	2.5	10.5 ± 0.2	4.9
20.0 ± 0.4	20.4 ± 0.3	1.8	20.4 ± 0.3	2.2	20.3 ± 0.3	1.4	20.7 ± 0.3	3.4
35.0 ± 0.6	34.9 ± 0.4	0.4	35.3 ± 0.4	0.7	35.2 ± 0.4	0.7	35.2 ± 0.4	0.6
50.0 ± 0.9	49.6 ± 0.4	0.8	49.2 ± 0.4	1.6	49.3 ± 0.4	1.3	49.1 ± 0.4	1.7

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