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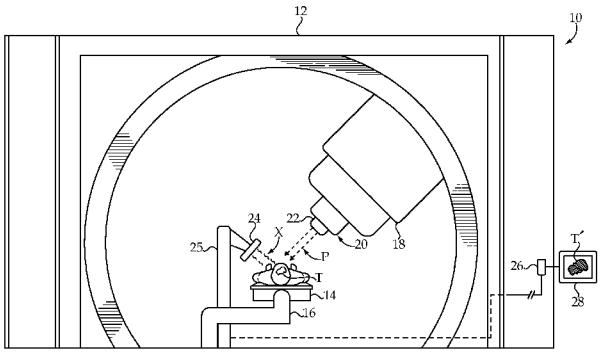

Fig.1

(57) Abstract: Chemotherapeutic agent within a tumor in a patient is detected by irradiating the tumor with a beam of protons, sensing X-rays emitted by chemotherapeutic agent in response to irradiation with the protons, and determining a value indicative of an amount of the chemotherapeutic agent, responsive to the sensed X-rays. A concentration of chemotherapeutic agent such as platinum based chemotherapeutic agent may be calculated based upon the determined value, such that adjusted chemotherapy or adjusted radiotherapy may be administered to a patient during concurrent chemotherapy and radiotherapy cancer treatment. A computerized system includes a computer coupled with an X-ray detector and configured to determine a value indicative of an amount of chemotherapeutic agent resident within a tumor responsive to an energy of sensed X-rays emitted by chemotherapeutic agent in response to irradiation with a beam of protons.

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Description

SYSTEM AND METHOD FOR CONCURRENT CHEMOTHERAPY AND RADIOTHERAPY CANCER TREATMENT, AND CHEMOTHERAPEUTIC AGENT DETECTION STRATEGY

Cross Reference To Related Applications

[0001] This Applications claims the benefit of the filing date of United States Provisional Patent Application Serial No. 61/622,576, filed April 11, 2012.

Technical Field

[0002] The present disclosure relates generally to the field of cancer treatment, and relates more particularly to detecting chemotherapeutic agent within a tumor via sensing X-rays emitted by the chemotherapeutic agent responsive to irradiating the tumor with a beam of protons.

Background

[0003] A variety of different radiotherapy treatments are used for treating cancer in human patients. In general terms, radiation in the form of photons or charged particles such as electrons, protons and ions, is applied to undesired tissue such as tumor tissue within a patient's body. Exposure of the undesired tissue to radiation causes cell death of targeted tissues in a well known manner. Chemotherapy treatments are also well known and widely used. Each of these treatment strategies has seen success, however, each has drawbacks. In the case of radiotherapy, some healthy tissue may be exposed to ionizing radiation in addition to the targeted, undesired tissue. In the case of chemotherapy, while the agents employed may be particularly toxic to tumor tissue, they are also toxic at least to some degree to

healthy tissue. Another challenge relating to effective cancer treatment with chemotherapy relates to the tendency for tumor cells to develop a resistance to chemotherapeutic agent over time.

[0004] In recent years, proposals to treat cancer with concurrent chemotherapy and radiotherapy have received increased attention. It is believed that radiotherapy can at least partially offset or compensate for resistance to chemotherapy developed by tumor cells. It is further believed that proton therapy, due to its capability of fairly tightly controlling exposure of tissue to ionizing radiation in a manner superior to photon radiotherapy, might be particularly effective in concurrent treatment strategies.

[0005] Radiation therapy often utilizes computerized tomography to identify geometric attributes of a tumor, enabling targeting of the radiation. In the case of concurrent treatment strategies, treatment planning based upon knowledge of the geometric attributes of a tumor typically takes place without any knowledge as to the present effects of chemotherapy administration. As a result, clinicians may formulate plans for the radiation component of concurrent therapy without full knowledge of how radiation might best be used to complement chemotherapy. This problem arises at least in part from the difficulty in deducing properties such as distribution or concentration of chemotherapeutic agent within the tumor. In some instances, penetration of chemotherapeutic agent into tumors may be non-uniform. Those skilled in the art will be familiar with the often chaotic vasculature which develops in tumor tissue, potentially resulting in widely varying perfusion such that one part of the tumor may receive plenty of chemotherapeutic agent, and another part of the tumor may receive virtually zero. Other issues are resistance to chemotherapeutic agent as noted above. Thus, understanding certain properties of chemotherapeutic drugs in vivo could provide clinicians with valuable insights into

how to further administer chemotherapy or radiation, however, techniques to assess such properties are not always possible or may be unsafe.

Summary

[0006] In one aspect, a method of detecting chemotherapeutic agent within a tumor in a patient includes irradiating the tumor with a beam of protons, and sensing X-rays emitted by a chemotherapeutic agent within the tumor in response to irradiation with the protons. The method further includes determining a value indicative of an amount of the chemotherapeutic agent, responsive to the sensed X-rays.

[0007] In another aspect, a method of concurrent chemotherapy and radiotherapy cancer treatment includes administering chemotherapy to a patient, and administering radiotherapy to the patient via irradiating a tumor within the patient via a therapeutic beam of protons. The method further includes sensing X-rays emitted by chemotherapeutic agent within the tumor in response to irradiating the tumor, and administering at least one of adjusted chemotherapy and adjusted radiotherapy to the patient based at least in part on an amount of the chemotherapeutic agent as indicated by the sensed X-rays.

[0008] In still another aspect, a system for treating cancer in a patient includes a proton beam nozzle positionable such that an emitted beam of therapeutic protons is directed towards a tumor within a patient. The system further includes an X-ray detector configured to sense X-rays emitted by a chemotherapeutic agent within the tumor in response to irradiation with the beam of therapeutic protons. The system further includes a computer coupled with the X-ray detector and being configured to determine a value indicative of an amount of chemotherapeutic agent resident within the tumor responsive to an energy of the sensed X-rays.

Brief Description of the Drawings

[0009] Figure 1 is a diagrammatic view of a treatment system according to one embodiment;

[0010] Figure 2 is a graph illustrating an intensity of X-rays emitted by chemotherapeutic agent resident within a tumor, at different energy levels; and

[0011] Figure 3 is a flowchart illustrating an example process according to the present disclosure.

Detailed Description

[0012] Referring to Figure 1, there is shown a system 10 for treating cancer in a patient. System 10 may be of a type suitable for proton radiotherapy, including a gantry 12 and treatment room wherein a patient support mechanism 14 is positioned. Patient support mechanism 14 may include a radiotherapy support table upon which a patient may be positioned for treatment in a conventional manner. A positioning arm 16 such as a robotic positioning arm may be mounted near gantry 12 such that patient support mechanism 14 can be moved about in essentially all possible degrees of freedom. A proton beam delivery mechanism 18 is mounted in or on gantry 12 and may be movable such that a beam of protons can be directed towards a treatment site within a patient from essentially any angle about 360°. Proton beam delivery mechanism 18 may be coupled with a suitable source of protons such as are commonly available at any proton radiotherapy treatment facility. Beam delivery mechanism 18 may further include a nozzle 20 having an aperture 22 coupled therewith, configured to control a shape of an emitted proton beam P. Those skilled in the art will be familiar with creation and manipulation of a beam of protons such that protons of varying energies comprise a therapeutic beam. Non-uniformity in the energy of protons emitted from nozzle 20 thus allows a tissue penetration depth of the protons to be tailored in accordance with the geometry of a tumor, having well

known advantages with regard to avoiding exposure of healthy tissue to ionizing radiation. Thus, a beam of protons P emitted from nozzle 20 may be controlled and shaped such that the emitted beam is directed towards a tumor within a patient in a targeted manner.

[0013] It has been discovered that a tendency for chemotherapeutic agent resident within a tumor in a patient to emit X-rays in response to interaction with protons can be leveraged to deduce information as to distribution and concentration of chemotherapeutic agent in a tumor which is useful in treating a patient. To this end, system 10 may further include a detector 24 configured to sense X-rays emitted by chemotherapeutic agent resident within a tumor T in a patient, in response to irradiation of the tumor with a beam of protons. Detector 24 may include any suitable commercially available or manufacturable X-ray detector. Detector 24 may be positioned upon and coupled with a detector support mechanism 25 mounted in gantry 12. Support mechanism 25 may be manipulated to position detector 24 at a range of orientations about a patient positioned upon support mechanism 14. In the illustrated embodiment, detector 24 is positioned and oriented to sense X-rays, shown via reference letter X, emitted approximately at an angle 90° from a direction of incidence of beam P. Thus, detector 24 will typically be positioned such that only a portion of X-rays emitted from the tumor will be sensed. Moreover, detector 24 will typically be configured/positioned such that its sensing field includes only a part of the tumor. Detector 24 could be positioned in contact with the patient, or nearly so, in certain instances. In certain embodiments, an array of detectors might be used to simultaneously, or at different times, sense X-rays emitted by chemotherapeutic agent resident within a tumor in a patient in response to irradiation with the protons. Detector 24 might be movable via mechanism 25 to detect X-rays at different angles relative to the direction of incidence of beam P, and/or for detecting X-rays emitted from different parts of tumor T.

[0014] System 10 may also include a computer 26 coupled with detector 24. A display 28 may be coupled with computer 26, and positioned outside of gantry 12 and the treatment room for viewing by a clinician. In one embodiment, computer 26 may be configured to determine a value indicative of an amount of chemotherapeutic agent resident within a tumor within a patient, or a part of the tumor, responsive to X-rays sensed via detector 24. The subject value may include a quantitative or qualitative numerical value. For instance, the determined value might correspond to detection of a high, medium, or low amount of chemotherapeutic agent. The determined value might alternatively have a value equal to zero if no chemotherapeutic agent is detected or if the amount detected is below a threshold, and could have a value equal to one if any chemotherapeutic agent at all is detected, or if the amount detected is at or above the threshold. In more quantitative approaches, the determined value might be a number of X-rays detected, an intensity of X-ray radiation at certain frequencies or energies, or some other value.

[0015] In one practical implementation strategy, computer 26 may further include a computer readable medium (not shown), and may be configured to store electronic data on the computer readable medium which is indicative of an intensity of X-ray radiation from a tumor in response to irradiation with the beam of therapeutic protons. Computer 26 may be further configured to determine the value discussed above responsive to the stored electronic data. The term "intensity" is used herein in a manner not to be confused with the term "energy." An X-ray photon will include and is often characterized by an energy level, typically expressed in electron-volts (eV). As will be further apparent from the following description, detection of X-rays having energies within one or more energy ranges enables a determination that the detected X-rays are in fact likely to have been emitted by chemotherapeutic agent in response to interaction with a proton. Thus, the term "energy" can be used to characterize one X-ray. The term "intensity" in contrast refers to overall strength of

X-ray radiation, thus, "intensity" may characterize more than one X-ray. Where a certain number of X-rays having certain properties, such as a given energy level, are detected, X-ray radiation at that energy or within a certain energy range might be said to have a given intensity. These principles and their exploitation will be further apparent from the following description.

[0016] Referring now to Figure 2, there is shown a graph illustrating an intensity of X-ray radiation emitted by platinum based chemotherapeutic agent resident within a tumor at different energy levels, in particular within three energy ranges. A first peak KL2, a second peak KL3, and a third peak KM3 each represent detection of X-ray radiation having certain photon energies, namely, about 62.5 keV, about 65 keV, and about 75 keV, respectively, in a case of the chemotherapeutic agent containing platinum (i.e. cisplatin). A height of the peaks represents an intensity of sensed X-ray radiation at or about those energy levels. Thus, KL2 is more intense than KM3, and KL3 is more intense that KL2.

[0017] Each of the peaks shown in Figure 2 may further be understood to represent detection of characterized X-rays, meaning X-rays which are known to result from, or be likely to result from, an interaction between a proton and a particular type of chemotherapeutic agent. Those skilled in the art will be familiar with platinum based chemotherapeutic agents such as cisplatin. In Figure 2, each of peaks KL2, KL3, and KM3, may be understood to represent detection of X-rays likely to have been emitted as a result of interaction between protons and the platinum within cisplatin. The stored electronic data discussed above might include the intensity data and energy level data depicted in Figure 2. In one embodiment, an empirically derived model may be used to calculate or estimate actual amount of chemotherapeutic agent indicated by the data as represented in Figure 2. An empirically derived model also might be used to calculate or estimate a relative amount of chemotherapeutic agent indicated by the data, such as a concentration.

[0018] Proton radiation therapy typically utilizes initial proton energies of up to 250 MeV. During treatment with the proton beam, the Spread Out Bragg Peak (SOBP) may be formed to cover the treatment target by utilizing a set of weighted proton beams of different initial energies. The average energy of protons in the area of the SOBP is a few tens of MeV. In the 20-100 MeV proton energy range, the cross section for K-shell ionization of high atomic number elements (Z=78 for platinum) exceeds several barns, reaching a maximum of about ten barns between 100 and 200 MeV.

[0019] The energies of characteristic X-ray lines of high atomic number elements such as platinum are significantly higher than those of low and middle atomic number elements typically present in tissue such as calcium, iron, iodine. This property allows one to distinguish Pt-characteristic X-rays both by separation of the lines in the spectral analysis and by different attenuation in tissue; while more than 10% of characteristic X-rays from platinum will typically penetrate 10 cm of tissue, the attenuation of iodine characteristic X-rays is higher by an order of magnitude, and the remaining characteristic radiation from elements of the tissue composition will tend to be completely absorbed.

[0020] For the detection of photons from the platinum K-group, High Purity Germanium (HPGe) detectors may offer the best energy resolution and high efficiency, maximizing the ability to identify platinum signal and differentiate it from background transitions from other tissue nuclides. The following estimate of expected counting rate for the proposed method of platinum determination in tumor is based on the parameters of semi-planar HPGe detector NIGP 2010470 from Princeton gamma-Tech, Inc. (PGT), with a 20 cm^2 active area and an energy resolution of 470 eV at 5.9 keV and 650 eV at 122 keV. Assuming a 1 liter tumor volume with platinum concentration of 10 μg/g, and with the center of the tumor located at a 10 cm depth in the body, while the detector is placed at the body surface,

the number of counts N_k, under the peaks of K group characteristic X-rays, per unit time, can be estimated as:

$$N_K = I_0 n_{Pt} \sigma_K G \varepsilon_K \beta_K ,$$

where I_0 is the number of protons incident on the target per unit time, and it can be determined from the expected dose of 2 Gy delivered in a 10x10 cm^2 field in 10 seconds. 1 Gy corresponds to (1.2-1.4)x10^9 protons/cm^2, hence $I_0 \approx 2.6 \times 10^{10}$ p/s. n_{Pt} is the number of Pt nuclei per unit area of the target, and can be estimated as:

$$n_{Pt} = m_{Pt} N_{av} / (A_{Pt} S),$$

where m_{Pt}=0.01 g is the estimated mass of platinum present in the tumor based on the assumption of Pt concentration of 10 μg/g and tumor mass of 1 kg; $N_{av}=6.02 \times 10^{23}$ is the Avogadro number; A_{pt}=195 is the Pt atomic mass and S=100cm^2 is the radiation field cross section, hence $n_{Pt}=3.1 \times 10^{17}$ nucl/cm^2. σ_K is the cross-section for K-shell ionization by the incident protons; $\sigma_K \approx 10b$ on average in the 10-200 MeV energy region. $G=1.6 \times 10^{-2}$ is the target detector geometry factor estimated as $G = S_{det} / (4\pi R^2)$, where S_{det}=20 cm^2 is the detector-sensitive area, R=10 cm is the distance between the target center and the detector. ε_K=0.9 is the intrinsic detector efficiency for a 1 cm thick detector at the energies corresponding to the peak locations. β_K=0.12 is the target self-absorption coefficient, averaged over the 65-75 keV energy range. The X–ray attenuation in the target may be estimated as $\beta_k = \exp(-(\mu/p)x)$; M/P=0.2 cm^2/g is X-ray mass attenuation coefficient for soft tissue, and x=10.6 g/cm^2 is the target (tissue) thickness in g/cm^2 (assuming tumor depth of 10 cm). Based on the above assumptions, the estimated $N_K \approx$ $2.6 \times 10^{10} \times 3.1 \times 10^{17} \times 10 \times 10 \times 10^{-24} \times 1.6 \times 10^{-2} \times 0.9 \times 0.12 = 1.4 \times 10^2$ counts /second, or 1.4×10^3 counts per treatment could be achieved. For small tumor and low Pt concentrations, sensitivity and accuracy could depend on the ability to separate

relatively small characteristic X-ray peaks from the continuous background during proton therapy treatment.

[0021] Returning to Figure 1, display 28 might be used to display a signal trace or the like similar to the graph shown in Figure 2. This would enable a clinician to visually and qualitatively monitor detection of X-rays emitted during the course of a proton radiotherapy treatment session. The clinician or a computer might also compare data obtained for one part of a tumor with data obtained for another part of a tumor, and thus deduce based on the intensity of sensed X-ray radiation a difference or similarity in amount of chemotherapeutic agent between different parts of the tumor. To this end, display 28 might display an image T' of a tumor within a patient, and graphically convey to a clinician such as via shading, coloring, etc., different amounts of chemotherapeutic agent resident within different parts of the tumor, such as is shown in the example tumor image T' in Figure 1. This capability represents an altogether new imaging modality.

[0022] As noted above, computer 26 may be configured to determine a value indicative of an amount of chemotherapeutic agent resident within a tumor, responsive to sensed X-rays. Since intensity of X-ray radiation at different photon energies or in different photon energy ranges may relate to a number of sensed X-rays having those photon energies or photon energy ranges, the value may be determined responsive to a number of sensed X-rays. Each time detector 24 senses, say, an X-ray of "z" keV, "z + 1 keV," or "z + 2 keV, the detection can be recorded. Sensing of the X-rays might take place over the entire course of a proton radiotherapy session, but might instead take place during only a portion of the session. In any event, however, the value may be determined responsive to a number of the sensed X-rays in a time step, whether that time step is an entire session or only a part thereof. Where X-rays are sensed in a plurality of photon energy ranges, similar to what is depicted in the graph of Figure 2, the value may be determined

responsive to a sum of the number of sensed X-rays in each of those pertinent photon energy ranges.

[0023] In any event, based upon the determined value, a concentration of chemotherapeutic agent within the tumor may be calculated. One example strategy for calculating a concentration of chemotherapeutic agent within part or all of a tumor. As noted above, the chemotherapeutic agent may include a platinum based chemotherapeutic agent and, hence, concentration of platinum based chemotherapeutic agent such as cisplatin in a part or all of a tumor is possible.

Industrial Applicability

[0024] Referring now to Figure 3, there is shown a flowchart 100 illustrating example steps in a process according to the present disclosure. The process of flowchart 100 may Start at step 110, and may then proceed to step 120 at which a tumor is irradiated with a beam of protons, such as a therapeutic beam of protons as discussed herein. From step 120, the process may proceed to step 130 to sense emitted X-rays such as by way of detector 24. From step 130, the process may proceed to step 140 to determine a value indicative of an amount of chemotherapeutic agent within the tumor, responsive to the sensed X-rays. From step 140, the process may proceed to step 150 to calculate concentration of the chemotherapeutic agent within the tumor based at least in part on the determined value. Determining a volume of the tumor for purposes of calculating the concentration can take place by way of known techniques. From step 150, the process may proceed to Finish at step 160.

[0025] The strategy disclosed herein for detecting chemotherapeutic agent may be used in a variety of ways. As discussed above, this general detection strategy can support an altogether new imaging modality, whereby a clinician can visually examine, and/or qualitatively compare concentration of chemotherapeutic agent in

different parts of a tumor. This capability enables a clinician to confirm that a chemotherapy treatment protocol is proceeding as desired, but can also give the clinician information sufficient to change the treatment protocol or make adjustments. In the case of concurrent chemotherapy and radiotherapy treatment of cancer, a clinician may choose to administer a chemotherapy dose to a patient according to some standard treatment protocol. A tumor which is to be treated may then be irradiated with a therapeutic beam of protons also according to some standard treatment protocol. X-rays emitted by the chemotherapeutic agent during irradiation with the protons may then be sensed, and the clinician can make a choice as to whether to continue the chemotherapy treatment as planned or whether to make adjustments. In one embodiment, treatment might proceed by administering an adjusted chemotherapy dose to a patient based at least in part on an amount of chemotherapeutic agent as indicated by sensed X-rays. Since the present disclosure enables calculating a concentration of the chemotherapeutic agent within a tumor, a clinician may choose to administer an adjusted chemotherapy dosage amount based upon the calculated concentration. In other embodiments, dosing frequency or even type of chemotherapeutic agent used might be changed during treatment based upon the information gleaned according to the presently disclosed strategies as to distribution and/or concentration of chemotherapeutic agent within a tumor. Still other measures available to a clinician could include adjusting the proton radiotherapy part of treatment, such as suspending or reducing proton radiotherapy where chemotherapeutic agent appears to have been aggressively absorbed by the tumor, or focusing proton radiotherapy upon parts of the tumor not appearing to be adequately penetrated by chemotherapeutic agent. One substantial advantage of the present disclosure is that heretofore unavailable information as to *in situ* effects and properties of chemotherapy treatment is obtained without subjecting a patient to any additional radiation, apart from what their treatment plan already requires.

[0026] The present description is for illustrative purposes only, and should not be construed to narrow the breadth of the present disclosure in any way. Thus, those skilled in the art will appreciate that various modifications might be made to the presently disclosed embodiments without departing from the full and fair scope and spirit of the present disclosure. Other aspects, features, and advantages will be apparent upon an examination of the attached drawings and appended claims.

Claims

What is claimed is:

1. A method of detecting chemotherapeutic agent within a tumor in a patient comprising the steps of:

irradiating the tumor with a beam of protons;

sensing X-rays emitted by a chemotherapeutic agent within the tumor in response to irradiation with the protons; and

determining a value indicative of an amount of the chemotherapeutic agent, responsive to the sensed X-rays.

2. The method of claim 1 further comprising a step of calculating a concentration of the chemotherapeutic agent within the tumor based at least in part on the determined value.

3. The method of claim 2 wherein the step of determining further includes determining the value responsive to a number of the sensed X-rays in a time step.

4. The method of claim 3 wherein the step of sensing further includes sensing X-rays in a plurality of energy ranges, and wherein the step of determining further includes determining the value responsive to a sum of the number of sensed X-rays in each of the energy ranges.

5. The method of claim 2 wherein the step of calculating includes calculating a concentration of platinum based chemotherapeutic agent.

6. The method of claim 1 wherein the step of irradiating includes irradiating the tumor with a therapeutic beam of protons.

7. A method of concurrent chemotherapy and radiotherapy cancer treatment comprising the steps of:

administering chemotherapy to a patient;

administering radiotherapy to the patient via irradiating a tumor within the patient with a therapeutic beam of protons;

sensing X-rays emitted by chemotherapeutic agent within the tumor in response to irradiating the tumor; and

administering at least one of adjusted chemotherapy and adjusted radiotherapy to the patient based at least in part on an amount of the chemotherapeutic agent as indicated by the sensed X-rays.

8. The method of claim 7 wherein the step of administering chemotherapy includes administering a platinum based chemotherapeutic agent.

9. The method of claim 8 further comprising a step of calculating a concentration of the chemotherapeutic agent within the tumor based at least in part on the determined value;

wherein the second administering step includes administering an adjusted dosage amount of the chemotherapeutic agent based at least in part on the concentration.

10. The method of claim 8 further comprising a step of recording electronic data indicative of an intensity of sensed X-rays having an energy indicative of emission by the platinum based chemotherapeutic agent.

11. The method of claim 7 wherein the step of sensing further includes sensing X-rays in a sensing field which includes a first part of the tumor, and the method further comprises a step of sensing X-rays in another sensing field which includes a second part of the tumor.

12. The method of claim 11 further comprising a step of comparing a first amount of the chemotherapeutic agent resident within the first part of the tumor with a second amount of the chemotherapeutic agent resident within the second part of the tumor.

13. The method of claim 12 wherein the step of comparing includes comparing a first concentration of the chemotherapeutic agent within the first part of the tumor with a second concentration of the chemotherapeutic agent within the second part of the tumor.

14. A system for treating cancer in a patient comprising:

a proton beam nozzle positionable such that an emitted beam of therapeutic protons is directed towards a tumor within a patient;

an X-ray detector configured to sense X-rays emitted by a chemotherapeutic agent resident within the tumor in response to irradiation with the beam of therapeutic protons; and

a computer coupled with the X-ray detector and being configured to determine a value indicative of an amount of chemotherapeutic agent resident within the tumor responsive to an energy of the sensed X-rays.

15. The system of claim 14 further comprising a computer readable medium, the computer being configured to store electronic data on the computer readable medium which is indicative of an intensity of X-ray emission from the tumor in response to irradiation with the beam of therapeutic protons, and further configured to determine the value responsive to the stored electronic data.

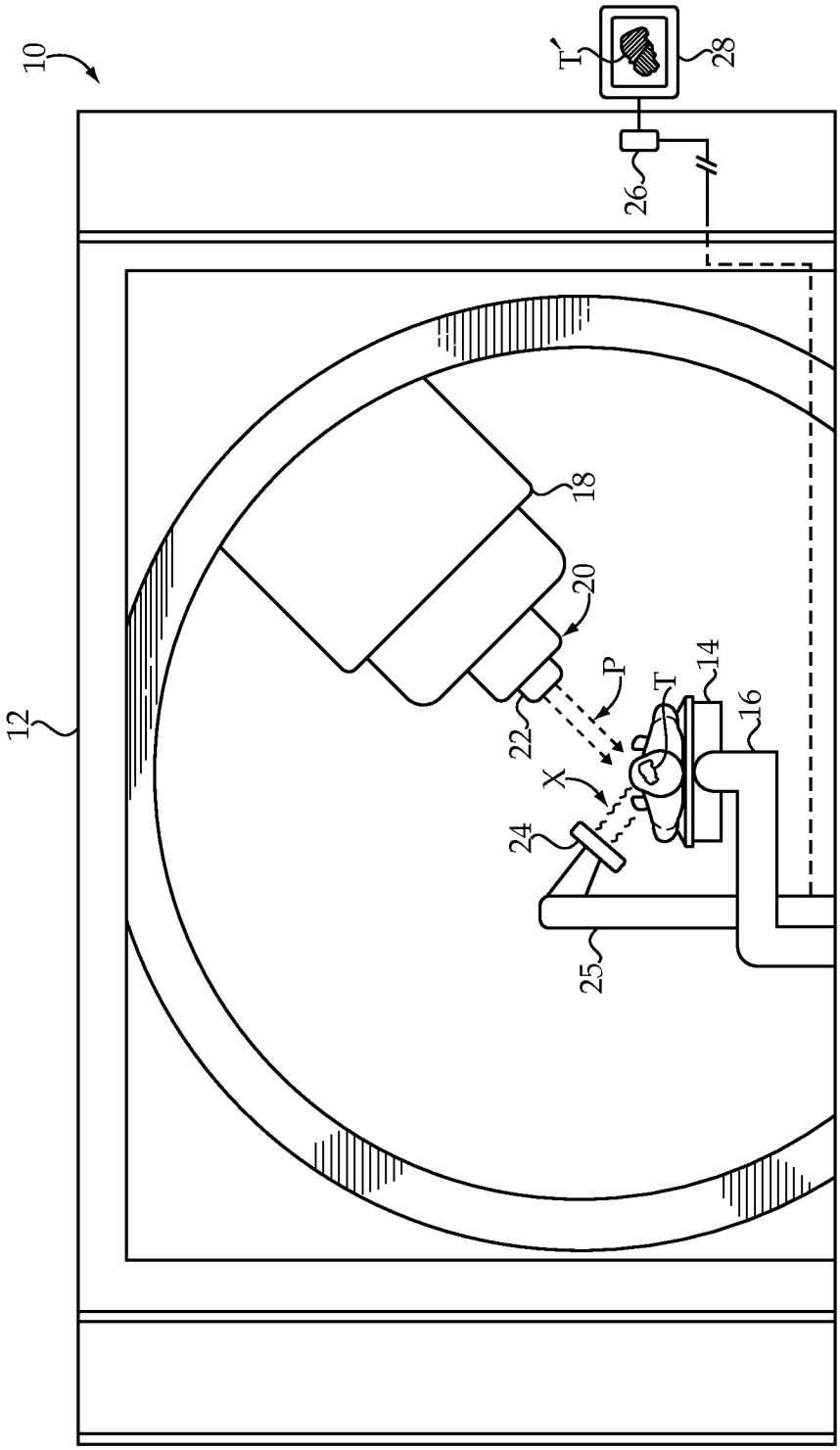

Fig.1

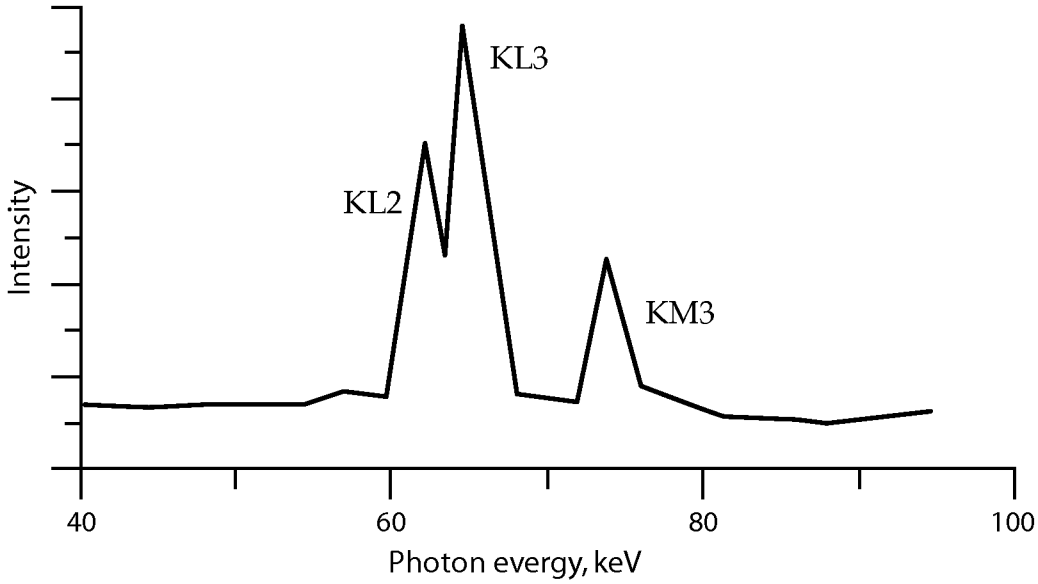
KL3
KL2
KM3
Intensity
40
60
80
100
Photon evergy, keV

Fig.2

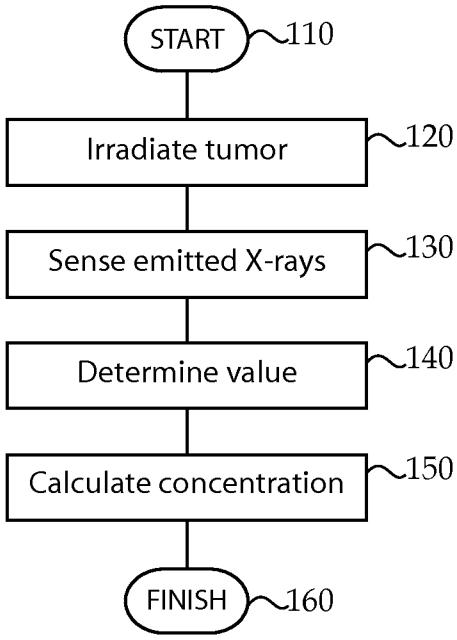
START
110
Irradiate tumor
120
Sense emitted X-rays
130
Determine value
140
Calculate concentration
150
FINISH
160

Fig.3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US13/35886

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61N 5/10, 5/00; A61B 5/05 (2013.01)
USPC - 600/2, 1, 407; 424/9.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8): A61N 5/10, 5/00; A61B 5/05 (2013.01)
USPC: 600/2, 1, 407; 424/9.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
MicroPatent (US-Granted, US-Applications, EP-A, EP-B, WO, JP, DE-G, DE-A, DE-T, DE-U, GB-A, FR-A); ScienceDirect; Pubmed; Google; Google Scholar; 'proton beam,' 'x-ray emission,' 'platinum based chemotherapeutic agents,' 'PIXE,' 'proton-induced x-ray emission,' chemotherapy

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☐ Further documents are listed in the continuation of Box C. ☐

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22 July 2013 (22.07.2013)	26 JUL 2013
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