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(54) **TREATMENT PLANNING SYSTEM FOR RADIOPHARMACEUTICALS**

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G06Q 50/22 (2018.01)
G06F 19/00 (2018.01)

(52) **U.S. Cl.**
CPC ***G06Q 50/22*** (2013.01); ***G06F 19/00*** (2013.01)

(58) **Field of Classification Search**
CPC A61K 2300/00; A61K 2039/545; G06Q 50/22
USPC 705/2–4; 378/65, 96
See application file for complete search history.

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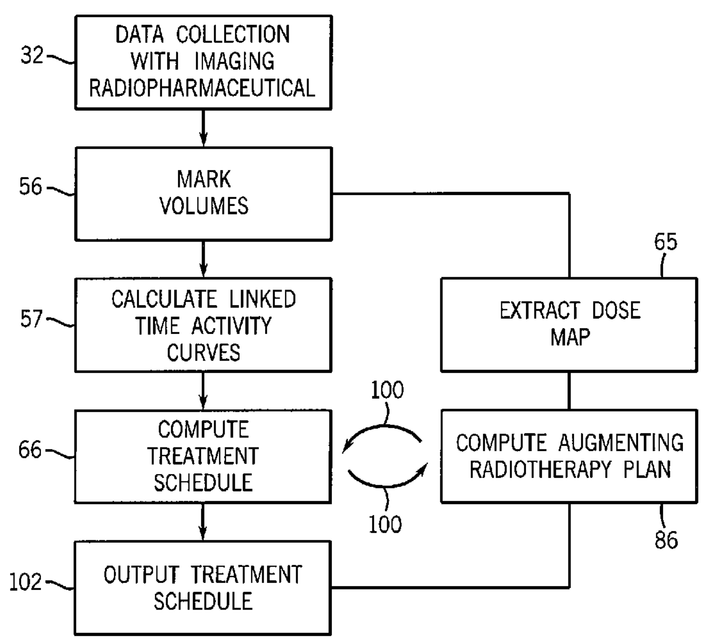
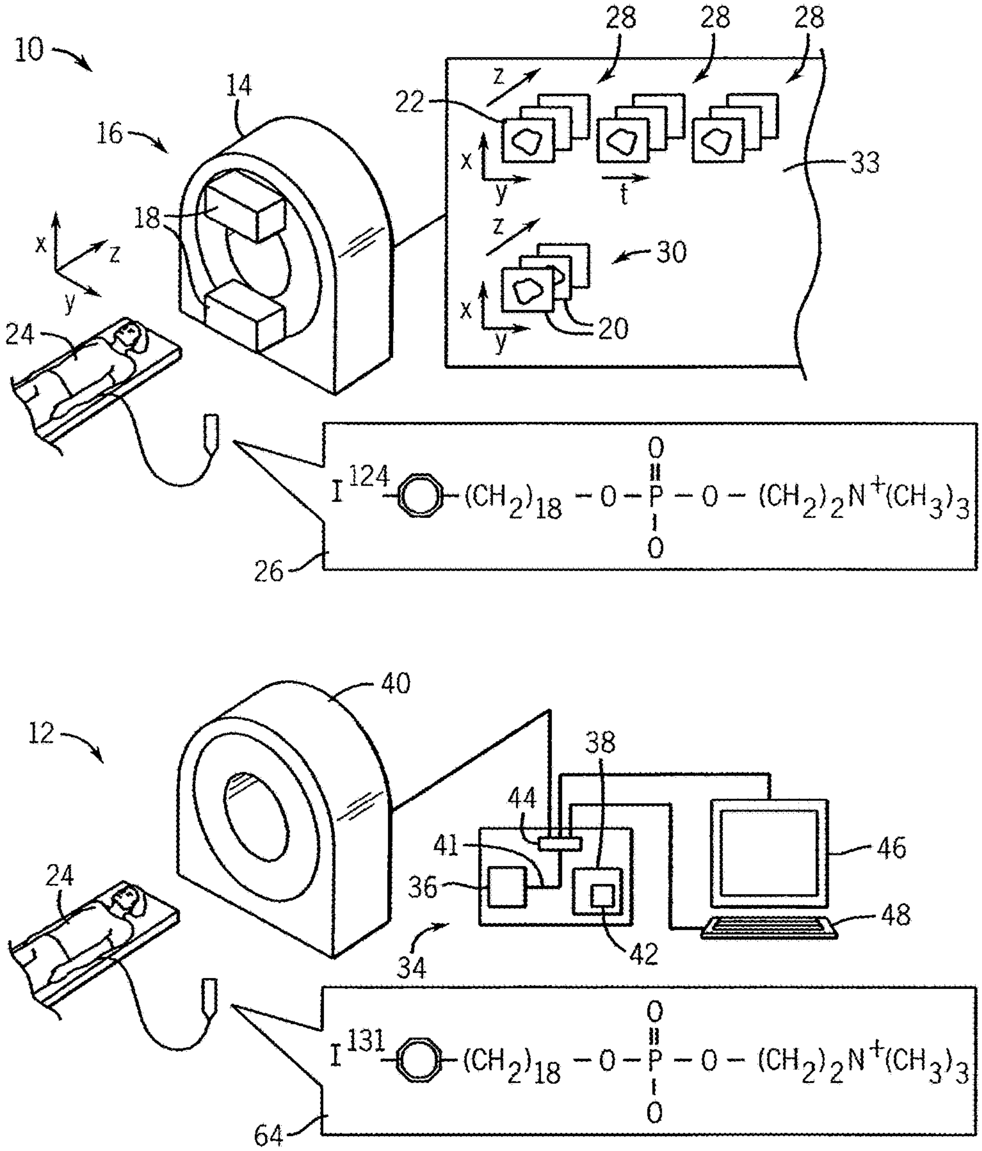
(57) **ABSTRACT**

A treatment schedule for radiopharmaceuticals is developed by collecting a volumetric history of tissue uptake in identified volumes of interest using emitted-radiation scans and relating this data to a treatment-radiopharmaceutical to develop a quantitatively accurate radiation treatment schedule of delivery amounts and delivery times of the treatment-radiopharmaceutical. This data may also be used to model biological effective dose and to prepare augmenting external radiation beam treatment schedules.

22 Claims, 3 Drawing Sheets

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16
14
18
22
28
28
28
z
x
y
t
33
z
30
x
y
20
x
z
y
24
26
I 124
(CH2)18 – O – P – O – (CH2)2N+(CH3)3
O
O
12
40
38
44
41
36
34
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46
48
24
64
I 131
(CH2)18 – O – P – O – (CH2)2N+(CH3)3
O
O

FIG. 1

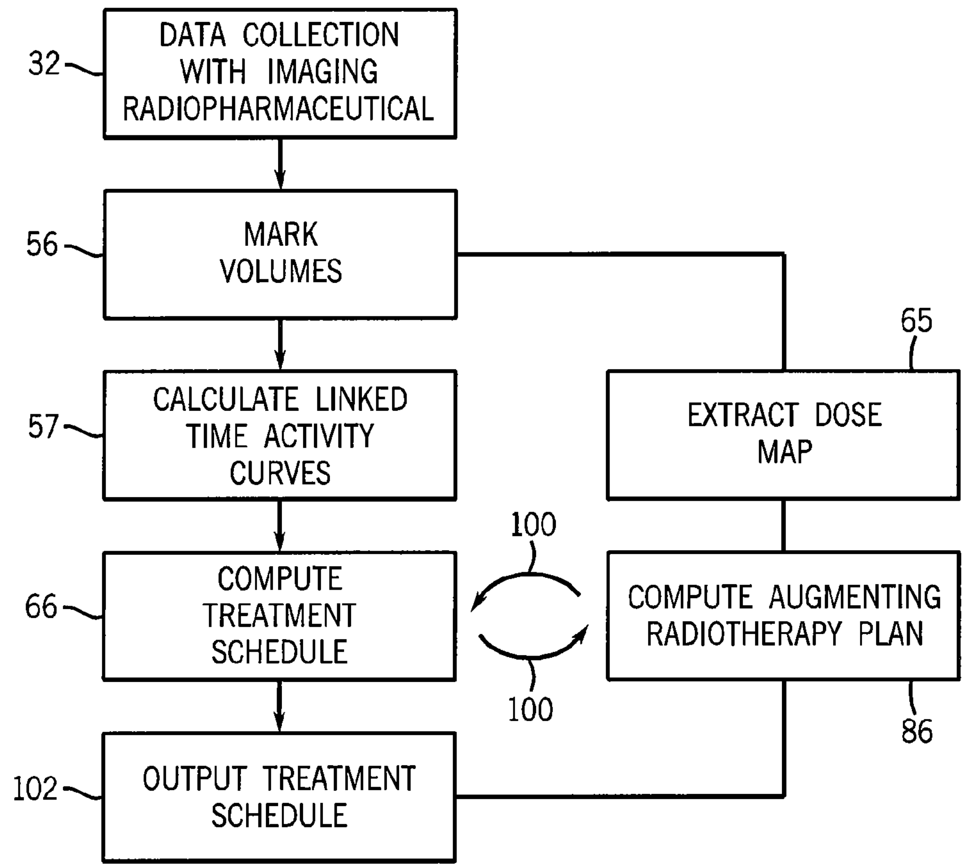
32
DATA COLLECTION WITH IMAGING RADIOPHARMACEUTICAL
56
MARK VOLUMES
57
CALCULATE LINKED TIME ACTIVITY CURVES
66
COMPUTE TREATMENT SCHEDULE
102
OUTPUT TREATMENT SCHEDULE
65
EXTRACT DOSE MAP
100
100
COMPUTE AUGMENTING RADIOTHERAPY PLAN
86

FIG. 2

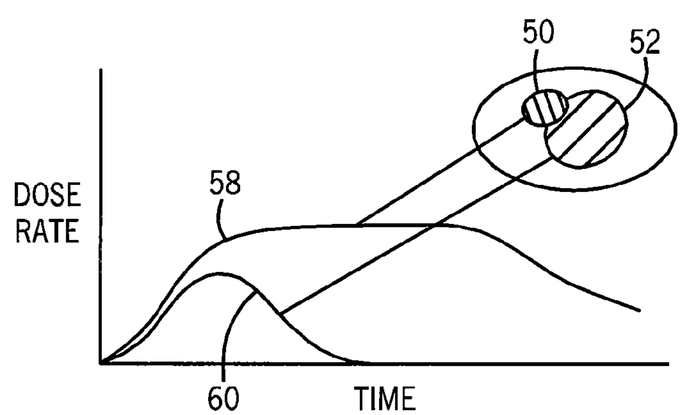
50
52
58
DOSE RATE
60
TIME

FIG. 3

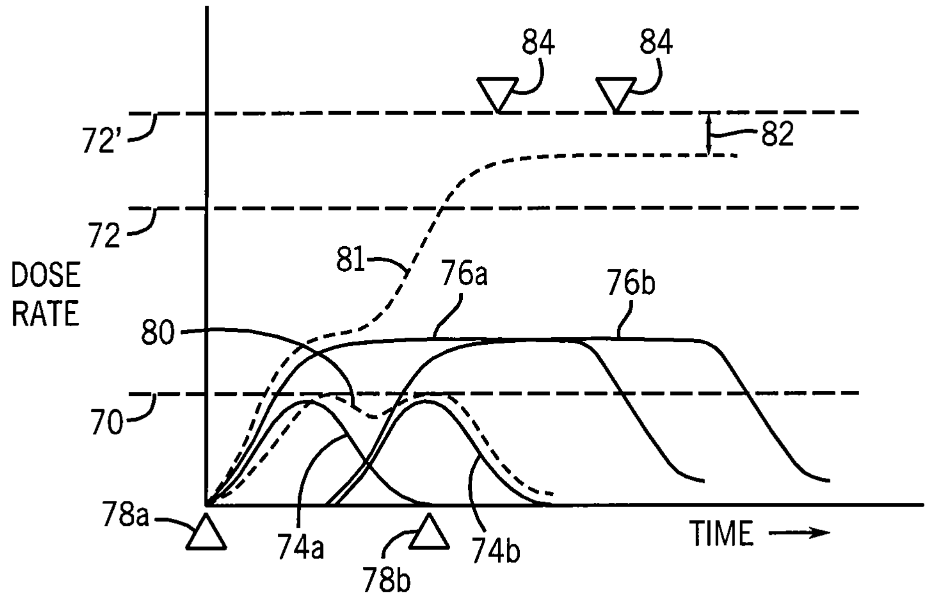
84
84
72'
82
72
81
76a
76b
DOSE
RATE
80
70
78a
74a
78b
74b
TIME

FIG. 4

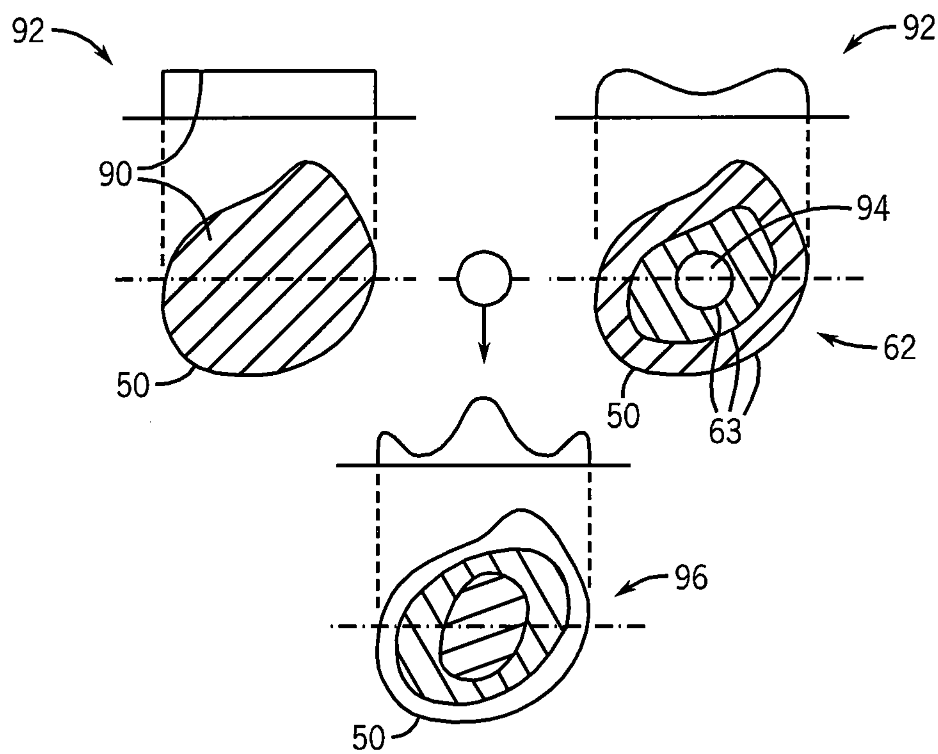
92
92
90
94
62
50
50
63
96
50

FIG. 5

TREATMENT PLANNING SYSTEM FOR RADIOPHARMACEUTICALS

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with United States government support awarded by the following agency:

NIH CA014520, CA109656

The United States government has certain rights in this invention.

BACKGROUND OF THE INVENTION

The invention relates generally to methods and apparatus for the treatment of tumors using radiopharmaceuticals and, in particular, to a system for the computerized scheduling of the administration of such radiopharmaceuticals.

Radiopharmaceuticals include materials that may "target" specific tissues to deliver radioactive materials to those targeted tissues. Such radiopharmaceuticals generally combine a radioactive component such as a radionuclide with a tracer component exhibiting selective uptake in target tissue. Such radiopharmaceuticals allow imaging or treatment of specific tissues in the body after a generalized introduction of the radiopharmaceutical to the body, for example, by injection into the bloodstream.

When such radiopharmaceuticals are used for radiation therapy, the quantity and timing of the administration of the radiopharmaceutical must provide a radiation dose to the tissue sufficient to kill tumor cells and the radiation dose must be sustained for a time period related to the reproduction rate of tumor cells. While the selective uptake of radiopharmaceuticals may concentrate the radioactive component in the target tissue, the selectivity of such mechanisms is not perfect and accordingly the quantity and timing of the administration of the radiopharmaceuticals must also be limited to reduce toxicity to healthy-tissues that exhibit some uptake of the radiopharmaceutical.

Selecting the appropriate quantity and timing for administration of a radiopharmaceutical may be approximated by using a model of a "standard man" or extrapolation from animal models such as rodents to humans. Differences between animals and humans and even among humans make such determinations imprecise at best.

SUMMARY OF THE INVENTION

The present invention provides a system for precisely tailoring the quantity and timing of the administration of a radiopharmaceutical to a particular patient. In one embodiment, the invention takes advantage of an analogous biological behavior between certain imaging and therapeutic radiopharmaceuticals. The imaging-radiopharmaceutical may be used to prepare "time activity curves" describing the uptake of the radiopharmaceutical in different designated volumes of interest using SPECT, PET or similar imaging modalities. The volumes of interest may be selected to include a target tissue and sensitive healthy-tissue. The collected time activity curves then form the basis for a model indicating uptake of a treatment-radiopharmaceutical. This model yields a precise, patient-specific treatment schedule for administering the radiopharmaceutical accommodating constraints such as minimum radiation dose-rate and healthy-tissue toxicity. This two-step technique can provide sufficient precision to make practical the combination of radiopharmaceutical treatment with other radiation treatment techniques such as external-beam radiotherapy.

Specifically then, the present invention permits the development of a treatment schedule for a treatment-radiopharmaceutical by using a three-dimensional data set recording a history of tissue uptake of an imaging-radiopharmaceutical in at least one volume of interest. This history of tissue (such as a time activity curve or TAC) shows the time during which the imaging-radiopharmaceutical is active in the volume of interest and may be used to prepare a treatment schedule for the treatment-radiopharmaceutical, the latter having similar uptake characteristics as the imaging-radiopharmaceutical. The treatment schedule provides a set of pharmaceutical delivery amounts and delivery times for the treatment-radiopharmaceutical.

It is thus a feature of at least one embodiment of the invention to employ current imaging technologies to provide quantitative guidance for therapeutic radiopharmaceuticals tailored for an individual patient.

The system may receive a desired treatment radiation dose-rate and the treatment schedule may determine radiopharmaceutical delivery amounts and delivery times to provide the desired treatment radiation dose-rate in the volume of interest.

It is thus a feature of at least one embodiment of the invention to use radiopharmaceutical imaging systems to develop an uptake model for that patient that may then be manipulated to produce an accurate treatment schedule.

In one embodiment, the invention deduces an active time of the imaging-radiopharmaceutical in at least two volumes of interest and the desired treatment radiation dose-rate is received for a first volume of interest and a toxicity limit is received for the second volume of interest. The delivery amount and delivery time of the treatment schedule is calculated to maximize a time period when the radiation dose-rate in the first volume of interest is no less than the desired treatment radiation dose-rate under the condition that the radiation dose-rate in the second volume of interest be no greater than the toxicity limit.

It is thus a feature of at least one embodiment of the invention to accurately model uptake and clearing time differences among tissue, particularly between treated and healthy-tissue, to provide the ability to make accurate trade-offs between tumor treatment and toxicity to healthy-tissue.

The invention may provide, in one embodiment, an augmenting radiation dose map for external-beam radiotherapy to augment a radiation dose in the first volume of interest when a desired treatment radiation dose-rate cannot be achieved under the condition that the radiation dose-rate in the second volume of interest is no greater than the toxicity limit.

It is thus a feature of at least one embodiment of the invention to promote a synergistic combination of external-beam radiotherapy and targeted radiopharmaceuticals by providing an improved model of radiopharmaceutical-induced radiation dose consistent with the accuracy provided by external-beam radiotherapy.

A library of toxicity limits for organs may be provided and the input volumes of interest may be organ names for the volumes of interest to automatically deduce the toxicity limits.

It is thus a feature of at least one embodiment of the invention to permit the treatment planner to identify volumes of interest as particular organs in order to provide for automatic optimization of delivery amount and delivery times for the radiopharmaceutical.

The system may determine the delivery amounts and delivery times by using a linear superposition of the active times of the imaging-radiopharmaceutical.

It is thus a feature of at least one embodiment of the invention to provide a highly versatile method of treatment planning for radiopharmaceuticals that allows a single imaging experiment to be used to construct a wide variety of different possible treatment plans.

The system may receive from a physician or other user a desired radiation dose map of the first volume of interest indicating the desired radiation dose in that volume of interest during a particular time. A cumulative radiation dose map of the first volume of interest may then be produced from the three-dimensional data set to compute a difference radiation dose therebetween for external radiation beam treatment.

It is thus a feature of at least one embodiment of the invention to address the problem of tumor hypoxia, or limited blood flow in some regions of a tumor, through the use of external-beam radiotherapy. The ability to treat the margins of the tumor with radiopharmaceuticals complements the ability of external-beam radiotherapy to treat a tumor center. The hypoxia introduces an increase oxygen enhancement ratio which has to be compensated for through increased radiation dose, thus combined therapies.

In one embodiment, the invention may compute an achievable external radiation beam radiation dose and iteratively correct the difference between radiation dose and the treatment schedule to provide a desired radiation dose to the first volume.

It is thus a feature of at least one embodiment of the invention to accommodate the physical limitations of external-beam radiotherapy by compensating with the radiopharmaceutical radiation dose and vice versa.

The imaging-radiopharmaceutical will typically be different from the treatment-radiopharmaceutical and accordingly the invention may include the step of correcting the active time schedule for the imaging-radiopharmaceutical to reflect an active time schedule of the treatment-radiopharmaceutical. This correction may change radiation dose-rate within the first and second volumes, for example reflecting different half-lives of different radionuclides, while preserving relative uptake between the first and second volumes.

It is thus a feature of at least one embodiment of the invention to permit imaging-radiopharmaceuticals to be used to develop precise models of the behavior of treatment-radiopharmaceuticals before the treatment-radiopharmaceuticals are used.

The imaging-radiopharmaceutical may be identical to the treatment-radiopharmaceutical with the exception of a radioactive isotope.

It is thus an object of the invention to test the same targeting mechanism that will be used with the treatment-radiopharmaceutical.

These particular features and advantages may apply to only some embodiments falling within the claims and thus do not define the scope of the invention.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic overview of the process implemented by the present invention;

FIG. **2** is a flow chart of the steps of the present invention as may be implemented in whole or in part on one or more electronic computers;

FIG. **3** is a graph showing a time activity curve collected using an imaging-radiopharmaceutical for two volumes of interest;

FIG. **4** is a graph showing development of a treatment plan for a treatment-radiopharmaceutical using the time activity curves of FIG. **3** as model elements; and

FIG. **5** is graphical representations of a desired radiation dose map and an actual radiation dose map produced by administration of the radiopharmaceutical, the difference providing a dose map for an augmenting external-beam radiation treatment plan.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

Referring now to FIG. **1**, the present invention provides a two-step process for the administration of a treatment-radiopharmaceutical having an imaging phase **10** followed by a treatment phase **12**.

In one embodiment, the imaging phase **10** uses a combination SPECT/CT or PET/CT machine **14**. Such a machine employs a conventional CT gantry **16** together with area gamma sensors **18** to provide a set of spatially aligned tomographic x-ray images **20** and corresponding tomographic emitted-radiation images **22** typically taken along a transverse (“x-y”) cross-sectional plane through the patient **24**. Tomographic x-ray images **20** and tomographic emitted-radiation images **22** displaced along the anterior-posterior (“z”) axis complete a three-dimensional data scan used by the present invention producing a volumetric CT image set **30** and a volumetric emitted-radiation image set **28**.

Contemporaneously with the CT scan, the patient **24** may be injected with a radiopharmaceutical **26**, for example, NM404 tagged with an imaging radionuclide I124. A description of this radiopharmaceutical **26** is found in U.S. patent application 2005/0196339 entitled: “Phospholipid Analogs As Diapeutic Agents and Methods Thereof”, published Sep. 8, 2005, naming the present inventor and hereby incorporated by reference. This particular radiopharmaceutical **26** emits gamma rays compatible with SPECT imaging.

As will be understood from the following discussion, the present invention is not limited to this particular radiopharmaceutical **26** or this particular radionuclide. Accordingly, the tomographic emitted-radiation images **22** may be collected using other radiopharmaceutical and with other imaging modalities, for example PET.

The collection of data of the volumetric emitted-radiation image set **28** continues for a period of time sufficient for the pharmacokinetic properties of the radiopharmaceutical **26** to be determined. Typically this period will be long enough for the radiopharmaceutical **26** to be taken up into the targeted tissue of the patient **24** and expelled from the body or to be exhausted by half-life decay. This time period will often span many days and, accordingly, the patient **24** may return to the hospital or clinic on a periodic basis for acquisition of each volumetric emitted-radiation image set **28**. Periodically in this process, a new volumetric CT image set **30** may be obtained (or selected tomographic x-ray images **20**) to, permit accurate alignment of the volumetric emitted-radiation image sets **28** with earlier and later data using the higher resolution CT data.

While the preferred embodiment employs x-ray CT data, it will be appreciated that other imaging modalities may be used in this capacity or that the volumetric emitted-radiation image set **28** may be used alone without a separate data set for alignment or volume definition as will be described below.

At the conclusion of this process a model data set **33** will have been collected including multiple volumetric CT image sets **30** and multiple volumetric emitted-radiation image sets **28**. Referring also to FIG. **2**, when the model data set **33** has been collected, as indicated by process block **32**, it may be loaded in a workstation **34**, for example, a free standing personal computer or a workstation associated with the SPECT/CT machine **14** or (as shown) associated with an external-beam radiation therapy machine **40**. The workstation **34** will preferably be of a type that can execute commercially available treatment planning software.

As is generally understood the art, such workstations **34** may include one or more processors **36** communicating with memory **38** by means of an internal bus **41**. The memory **38** may hold a program **42** implementing one or more steps of the present invention as well as data libraries, as will be described. The bus **41** may communicate with an interface **44** providing for graphics display on monitor **46** and the entry of data through keyboard **48** or the like. The interface **44** may also provide data to the external-beam radiation therapy machine **40** or receive data (not depicted) from the SPECT/CT machine **14**.

Referring now to FIGS. **2** and **3**, the model data set **33** may be loaded into memory **38** and displayed using conventional techniques to allow volumes of interest (VOIs) within the tissue to be identified with respect to the CT images. For example, a first tumor volume of interest **50** (tumor VOI) and an adjacent healthy-tissue volume of interest **52** (healthy-tissue VOI) may be identified. This identification describes a three-dimensional volume and may be performed, for example, by the reviewing of successive tomographic x-ray images **20** of the patient and a drawing of an outline around the particular volumes of interest. This process establishes x-y boundaries for each tomographic x-ray image **20** and multiple x-y boundaries over different images along the z-axis established by the remaining dimension of the VOI. The marking of the volumes of interests will typically be with respect to the volumetric CT image set **30** but may be informed by the data of the volumetric emitted-radiation image set **28** as well or may use the volumetric emitted-radiation image set **28** alone.

Upon completion of the definition of the volumes of interest, as indicated by process block **56**, the program may proceed to process block **57** where time activity curves are calculated for each of the volumes so identified. Time activity curves provide instantaneous radiation dose-rates as a function of time and the integral or area under the time activity curves provides total radiation dose.

This calculation process first segregates data elements of the volumetric emitted-radiation image set **28** to one of the volumes of interest **50** and **52** for each time period associated with the acquisition of the volumetric emitted-radiation image set **28**. The emitted-radiation in each data element of a given volume of interest **50** and **52** for a particular time is then convolved with a radiation dose point kernel to define the dose-rate for that time period. Together, the dose-rates for the different time periods provide time activity curve **58** (tumor TAC) associated with tumor VOI **50** and healthy-tissue time activity curve **60** (healthy-tissue TAC) associated with healthy-tissue VOI **52**. The radiation dose point kernel may be density corrected (using tissue density derived from the CT scan or the like). Other methods for determining dose rate may also be used including but not limited to a Monte Carlo dose calculation and similar techniques.

As depicted in FIG. **3**, the healthy-tissue TAC **60** associated with tissue that is not targeted by the radiopharmaceutical **26** will generally exhibit lower uptake (indicated by the lower peak of the healthy-tissue TAC **60**) and a shorter activity time (indicated by the shorter duration of the peak of healthy-tissue TAC **60**). In contrast, the targeting effect of the radiopharmaceutical **26** with respect to the tumor cells in the tumor VOI **50** results in a higher peak for tumor TAC **58** and a far longer duration as the radiopharmaceutical **26** is held in the tissues.

Referring now momentarily to FIG. **5**, as shown by process block **65**, at the time of computation of the tumor TAC **58** and the healthy-tissue TAC **60**, a radiation dose map **62** of tumor VOI **50** may be developed providing multiple iso-radiation dose lines **63** indicating the radiation dose received within the tumor VOI **50**. This dose map **62** may be a single map obtained by integrating the total radiation dose of the tumor VOI **50** for each volume element of the data set **33** within the tumor VOI **50** for the entire time of the tumor TAC **58**, or may be a set of dose maps associated with each volumetric emitted-radiation image set **28**. The use of this dose map **62** will be described below.

Referring now again to FIG. **1**, during the second treatment phase **12** of the present invention, the patient **24** will be injected with a treatment-radiopharmaceutical **64**. In this example, the treatment-radiopharmaceutical **64** is an NM404 with the radionuclide I131 or I125 substituted for I124. As will be understood, the present invention is not limited to this particular treatment-radiopharmaceutical **64** or this particular radionuclide nor is it necessary that the radiopharmaceutical **64** be suitable for imaging.

Generally, the radionuclide used in the treatment-radiopharmaceutical **64** will have a longer half-life than that used with the imaging-radiopharmaceutical **26** however; the same tracer component may be used to provide comparable uptake mechanisms. The treatment-radiopharmaceutical **64** will be administered to the patient **24** in a treatment schedule providing for delivery amounts and delivery times of the treatment-radiopharmaceutical **64** as computed by the present invention per process block **66** of FIG. **2**.

Referring now to FIG. **4**, the treatment schedule may be automatically calculated using a few setting parameters input by a clinician. The first parameter is a toxicity limit **70** for tissue in one or more healthy-tissue VOIs **52**. The toxicity limit **70** may be, for example, automatically provided from a stored library of toxicity limits associated with particular organs and the clinician may simply assign an organ name to each of the healthy-tissue VOIs **52**. When multiple healthy-tissue VOIs **52** have been identified with toxicity limit **70**, a treatment schedule will be calculated to keep the radiation dose-rate below the toxicity limit **70** of all of the healthy-tissue VOIs **52**. Alternatively, the absorbed dose, being the integral of the TAC **58**, may be kept below the toxicity limit **70** expressed as an absorbed dose.

The clinician may also enter a desired radiation dose-rate **72** for the tumor VOI **50**. This desired radiation dose-rate is set to provide a given minimum dose rate necessary to kill the tumor cells. Additionally, the clinician may enter a dose duration time indicating the desired length of treatment.

The time activity curves, shown in FIG. **3**, are now adjusted to account for the different radionuclide used in the imaging-radiopharmaceutical **26** versus the treatment-radiopharmaceutical **64** to provide a healthy-tissue model curve **74** and a tumor model curve **76**, conforming generally in shape to the healthy-tissue TAC **60** and the tumor TAC **58** adjusted in scale and possibly duration. The healthy-tissue model curve **74** and a tumor model curve **76** will be associated with a normalized treatment amount of the treatment-radiopharmaceutical **64** and can be simply scaled to accommodate different treatment quantities.

Using this principle, the healthy-tissue model curve **74***a* may be used to determine an administered quantity of the treatment-radiopharmaceutical **64** at a first radiopharmaceutical application **78***a* so that the peak of the healthy-tissue model curve **74***a* stays below the toxicity limit **70** for that tissue.

A second radiopharmaceutical application **78***b* may then be timed so that the sum (linear superposition) of the healthy-tissue model curve **74***b* for the second radiopharmaceutical application **78***b* and the healthy-tissue model curve **74***a*, being healthy-tissue rate total **80**, stay below the toxicity limit **70**.

Using these administered quantities, a corresponding tumor tissue rate total **81** can be determined by summing tumor model curves **76***a* and **76***b* associated with the radiopharmaceutical applications **78***a* and **78***b* in a manner similar to that used to produce healthy-tissue rate total **80**. As a result of the longer retention time of the treatment-radiopharmaceutical **64** in the tumor tissue of tumor VOI **50**, the tumor tissue rate total **81** continues to climb during this time to exceed the desired radiation dose-rate **72** while the healthy-tissue rate total **80** is constrained below the toxicity limit **70**. In this way, either manually or automatically, an optimized schedule of the times of radiopharmaceutical applications **78** and quantities of the treatment-radiopharmaceutical **64** administered at those times can be determined. This schedule pattern may be repeated to provide the necessary duration of treatment time defined by the time during which the tumor tissue rate total **81** exceeds desired radiation dose-rate **72**.

Referring still to FIG. **4**, in some cases the desired radiation dose-rate **72'** may exceed a peak level of the tumor tissue rate total **81** obtainable in the tumor VOI **50** while observing the toxicity limit **70** in the healthy-tissue VOI **52**. Accordingly, the present invention may calculate an augmenting dose that may be output to the external-beam radiation therapy machine **40** to provide an augmenting radiation dose to the tumor VOI **50** to correct for a shortfall **82** in the dose-rate in the tumor VOI **50**. The modeling system of the present invention allows precision in definition of the dose rate in particular volumes of interest **50** and **52** consistent with performing this type of augmentation by external-beam radiation therapy machines **40**. Normally external-beam radiotherapy and targeted radionuclide therapy have quite different dose rates and accordingly their doses are added by conversion of both to a common "biologically effective dose" (BED). BED effectively normalizes both of these processes into infinitesimally small fractions. As shown in FIG. **4**, this fractionation of the external radiation beam may be implemented by applying a radiation beam at multiple fractionation times **84** using the external-beam radiation therapy machine **40**.

Referring again to FIG. **2**, the computation of an augmenting radiation therapy plan shown generally by process block **86** may also be used to address a lack of uniformity in the radiation dose to the tumor VOI **50** by the treatment-radiopharmaceutical **64**. Referring again to FIG. **5**, the user may enter a desired radiation dose **90** to be received by the tumor VOI **50** here shown as a constant value in a cross section **92** through the tumor VOI **50**. As computed at process block **65**, lack of vascularization of the tumor tissue in the tumor VOI **50** (tumor hypoxia) may cause a lower radiation dose in a central region **94** of the tumor shown in a representative cross-section **92'**.

The process of providing information to the external-beam radiation therapy machine **40** for this augmenting treatment made employ a subtraction of the actual radiation dose of the tumor VOI **50** defined by iso-radiation dose lines **63** (adjusted to accommodate the change of radiopharmaceutical **64** from radiopharmaceutical **26**) from the desired radiation dose **90** to produce a difference dose **96** which can provide a desired radiation dose pattern for conventional treatment planning software for the external-beam radiation therapy machine **40**.

Referring again to FIG. **2**, this process of augmentation of the action of the radiopharmaceuticals with an external radiation beam may be performed iteratively with the actual radiation dose produced by the external-beam radiation therapy machine **40** being modeled and added to the radiation dose described by the iso-radiation dose lines **63** computed at process block **65**. A new difference dose **96** may then be computed and used to adjust either the treatment schedule for the radiopharmaceutical **64** or the dose provided by the external-beam radiotherapy machine **40** as indicated by iteration arrows **100**.

At process block **102**, an output is provided consisting of a set of delivery amounts and delivery times for the radiopharmaceutical **64** and scheduled times and dose patterns for external-beam radiation. It will be understood that other of treatment planning outputs may also be provided including an indication of total dose and other graphic elements depicting the treatment planning process of the present invention including for example an estimated total dose or time activity curves for the treatment radiopharmaceutical **62** in each region of interest.

It will be appreciated that the present invention permits implementation of radiobiological monitoring, for example, using the Linear Quadratic Model and the determination of biological effective doses (BED). By incorporating the Lea-Catcheside factor into the biological effective dose equation, it is possible to set the desired radiation dose-rate **72** to include the radiobiological effects of radiation dose-rate and sub-lethal repair of both early and late responding tissues.

It is specifically intended that the present invention not be limited to the embodiments and illustrations contained herein, but include modified forms of those embodiments including portions of the embodiments and combinations of elements of different embodiments as come within the scope of the following claims.

We claim:

1. A system for planning a treatment schedule for a treatment-radiopharmaceutical, the system comprising:

a radiation imaging machine adapted to scan a patient over a volume to measure emitted radiation;

an electronic computer communicating with the radiation imaging machine and executing a stored program held in non-transitory computer readable medium to:

(1) receive a three-dimensional data set from the radiation imaging machine indicating a history of tissue uptake of an imaging-radiopharmaceutical in at least one volume of interest;

(2) deduce an active time of the imaging-radiopharmaceutical in the volume of interest, the active time in the form of a measured time activity curve providing radiation dose rate as a function of time over a treatment period for the at least one volume of interest; and

(3) prepare a treatment schedule for a treatment-radiopharmaceutical different from the imaging-pharmaceutical, based on the active time of the imaging-radiopharmaceutical, the treatment schedule providing a schedule of multiple delivery amounts and delivery

times for the treatment-radiopharmaceutical, the treatment schedule setting the multiple delivery amounts and delivery times according to a combining of multiple overlapping values of multiple time activity curves spanning the treatment schedule, the multiple time activity curves each based on the measured time activity curve, each of the multiple time activity curves referenced to one of the delivery amounts and delivery times, the delivery amounts and delivery times constrained by a requirement that an overlapping radiation dose rate from a combination of the multiple time activity curves referenced to the delivery amounts and delivery times remains above a desired radiation dose rate necessary to kill tumor cells based on the active time of the treatment-radiopharmaceutical deduced from the active time of the imaging radiopharmaceutical.

2. The system of claim **1** wherein the program receives a desired treatment radiation dose-rate and the treatment schedule determines radiation dose and delivery time to provide the desired treatment radiation dose-rate in the volume of interest.

3. The system of claim **2** wherein the program deduces an active time of the imaging-radiopharmaceutical in at least two volumes of interest and wherein the desired treatment radiation dose-rate is received for a first volume of interest and the program further receives a toxicity limit for a second volume of interest and wherein the program determines radiation dose and delivery time to maximize a time period when the radiation dose-rate in the first volume of interest is no less than the desired treatment radiation dose-rate under a condition that the radiation dose-rate in the second volume of interest be no greater than the toxicity limit.

4. The system of claim **3** wherein the program provides an augmenting radiation dose map for external-beam radiotherapy to augment a radiation dose in the first volume of interest when a desired treatment radiation dose-rate cannot be achieved under the condition that the radiation dose-rate in the second volume of interest be no greater than the toxicity limit.

5. The system of claim **3** further including a library of toxicity limits for organs and wherein the program accepts as inputs volumes of interest and organ names for the volumes of interest to automatically deduce toxicity limits for the input volumes of interest.

6. The system of claim **2** wherein the program further receives a desired radiation dose map of the first volume of interest and determines a radiation dose map of the first volume of interest from the three-dimensional data set to compute a difference radiation dose therebetween for augmenting external radiation beam treatment.

7. The system of claim **6** wherein the program further computes an achievable external radiation beam radiation dose and iteratively corrects the difference radiation dose and the treatment schedule to provide a desired radiation dose to the first volume of interest.

8. The system of claim **2** wherein the imaging-radiopharmaceutical is different from the treatment-radiopharmaceutical and including the step of correcting the active time for the imaging-radiopharmaceutical to reflect an active time of the treatment-radiopharmaceutical.

9. The system of claim **8** wherein the step of correcting changes absolute uptake within the first and second volumes of interest while preserving relative uptake between the first and second volumes.

10. The system of claim **1** wherein the program further outputs an image showing an expected radiation dose to the first volume of interest.

11. The system of claim **1** wherein the program determines the delivery amounts and delivery time by using a linear superposition of the active time of the imaging-radiopharmaceutical.

12. A method for planning a treatment schedule for a treatment-radiopharmaceutical comprising the steps of:

(a) collecting three-dimensional data on a radiation imaging machine related to emitted radiation from an imaging radiopharmaceutical;

(b) collecting from the three-dimensional data collected in step (a) on at least one electronic computer executing a stored program stored in non-transitory computer readable medium, a three-dimensional data set indicating a history of tissue uptake of the imaging-radiopharmaceutical in at least two volumes of interest;

(c) determining on at least one electronic computer executing a stored program stored in non-transitory computer readable medium, uptake of the imaging-radiopharmaceutical in the two volume of interest over a period of time, the determined uptakes being in the form of measured time activity curves providing radiation dose rates as a function of time over a treatment period for the at least two volumes of interest; and

(d) preparing on at least one electronic computer executing a stored program stored in non-transitory computer readable medium, a treatment schedule for a treatment-radiopharmaceutical different from the imaging-pharmaceutical, the schedule providing multiple delivery amounts and delivery times based on a combining of multiple overlapping values of multiple time activity curves spanning the treatment schedule, the multiple time activity curves each based on one of the measured time activity curves, each of the multiple time activity curves referenced to different of the delivery amounts and delivery times; the delivery amounts and delivery times of the treatment schedule selected to maximize an uptake in the first volume of interest above a desired radiation dose rate necessary to kill tumor cells from a combination of overlapping radiation dose rates of the multiple delivery amounts subject to controlling uptake in the second volume of interest during the schedule below a toxicity limit.

13. The method of claim **12** wherein the imaging-radiopharmaceutical is identical to the treatment-radiopharmaceutical with an exception of a radioactive isotope.

14. The method of claim **12** wherein the imaging and treatment-radiopharmaceutical are different radioisotopes attached to NM404.

15. The method of claim **12** wherein the three-dimensional data set is collected by an imaging machine selected from the group consisting of: a SPECT imager and a PET imager.

16. The method of claim **12** further including the step of calculating an augmenting radiation dose map for external-beam radiotherapy to augment a radiation dose in the first volume of interest when ,a desired treatment radiation dose-rate cannot be achieved under a condition that the radiation dose-rate in the second volume of interest be no greater than the toxicity limit.

17. The method of claim **12** further including the step of receiving a desired radiation dose for the first volume and calculating a radiation dose map of the first volume of interest from the three-dimensional data set to compute a difference radiation dose and using the different radiation dose to calculate an augmenting radiation dose map for external-beam radiotherapy.

18. The method of claim **17** wherein the program first computes an achievable external radiation beam radiation dose and iteratively corrects the difference radiation dose and the treatment schedule to provide a desired radiation dose to the first volume.

19. The method of claim **12** wherein the imaging-radiopharmaceutical is different from the treatment-radiopharmaceutical and including the step of correcting the active time schedule for the imaging-radiopharmaceutical to reflect an active time schedule of the treatment-radiopharmaceutical, and wherein the step of correcting changes absolute uptake within the first and second volumes while preserving relative uptake between the first and second volumes.

20. The method of claim **12** wherein the method further outputs an image showing an expected radiation dose to the first volume.

21. The method of claim **12** further including the step of injecting the treatment-radiopharmaceutical.

22. A system for planning a treatment schedule for a treatment-radiopharmaceutical, the system comprising:

a radiation imaging machine adapted to scan a patient over a volume to measure emitted radiation;

an external-beam radiation therapy machine;

an electronic computer communicating with the radiation imaging machine and executing a stored program held in non-transitory computer readable medium to:

(1) receive a three-dimensional data set from the radiation imaging machine indicating a history of tissue uptake of an imaging-radiopharmaceutical in at least one volume of interest;

(2) deduce an active time of the imaging-radiopharmaceutical in the volume of interest, the active time in the form of a measured time activity curve providing radiation dose rate as a function of time over a treatment period for the at least one volume of interest;

(3) prepare a treatment schedule for a treatment-radiopharmaceutical different from the imaging-pharmaceutical, based on the active time of the imaging-radiopharmaceutical, the treatment schedule providing a schedule of multiple delivery amounts and delivery times for the treatment-radiopharmaceutical, the treatment schedule setting the multiple delivery amounts and delivery times according to a combining of multiple overlapping values of multiple time activity curves spanning the treatment schedule, the multiple time activity curves each based on the measured time activity curve, each of the multiple time activity curves referenced to one of the delivery amounts and delivery times, the delivery amounts and delivery times constrained by a requirement that an overlapping radiation dose rate from a combination of the multiple time activity curves referenced to the delivery amounts and delivery times remains above a desired radiation dose rate necessary to kill tumor cells based on the active time of the treatment-radiopharmaceutical deduced from the active time of the imaging radiopharmaceutical; and

(4) receive a desired radiation dose map of the volume of interest and determine a radiation dose map of the volume of interest from the three-dimensional data set to compute a difference radiation dose therebetween to provide to the external-beam radiation therapy machine.

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