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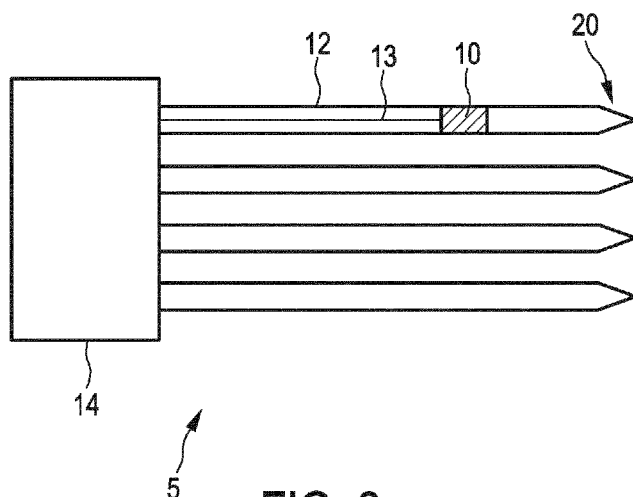


FIG. 2

(57) Abstract: The invention relates to a system for applying radiation to a target region within a subject. An introduction element (12) like a brachytherapy catheter is inserted into the subject and a radiation source (10) is moved within the introduction element such that it is located within or close to the target region. The target region is heated, wherein the movement of the radiation source within the introduction element is controlled depending on the temperature along the introduction element. The susceptibility of the subject for the radiation emitted by the radiation source at a respective location along the length of the introduction element can depend on the temperature at the respective location such that by controlling the movement of the radiation source depending on the temperature along the length of the introduction element the application of the radiation can be optimized.

System for applying radiation to a target region within a subject

FIELD OF THE INVENTION

The invention relates to a system, method and computer program for applying radiation to a target region within a subject.

5 BACKGROUND OF THE INVENTION

A system for applying radiation to a target region within a subject is, for instance, a high dose rate (HDR) brachytherapy system. An HDR brachytherapy system comprises a brachytherapy catheter which is introduced into the target region, wherein within the brachytherapy catheter a radioactive radiation source is moved to different dwell
10 positions at which the radioactive radiation source is located for respective dwell times. The target region is treated by radioactive radiation emitted by the radioactive radiation source at the different dwell positions for the respective dwell times.

The radiation emitted by the radiation source destroys, for instance, cancerous tissue primarily through the generation of oxygen radicals that attack the tumor DNA Cells to
15 be destroyed may only contain a relatively low amount of oxygen, which may lead to a reduced effectiveness of the application of the radiation.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide a system, method and
20 computer program for applying radiation to a target region within a subject, wherein the effectiveness of the application of the radiation can be improved.

In a first aspect of the present invention a system for applying radiation to a target region within a subject is presented, wherein the system comprises:

- an elongated introduction element for being inserted into the subject and for
25 introducing a radiation source emitting radiation to be applied to the target region into the subject,
- a moving unit for moving the radiation source within the introduction element such that the radiation source is located within or close to the target region,
- a heating unit for heating the target region,

- a temperature determination unit for determining the temperature along the length of the introduction element, and
- a control unit for controlling the moving unit depending on the determined temperature.

5 The susceptibility of the subject for the radiation emitted by the radiation source at a respective location along the length of the introduction element can depend on the temperature at the respective location. For instance, if the subject is a living being like a person or an animal, the applied radiation can be more effective, if the irradiated region has an increased oxygen level, wherein such an increased oxygen level can be achieved by
10 heating, because this will lead to a higher blood circulation and oxygen supply. Thus, determining the temperature along the length of the introduction element and controlling the movement of the radiation source within the introduction element depending on the determined temperature allows for an optimized effect of the application of the radiation.

 The heating unit may be adapted to heat the target region by microwave,
15 radiofrequency and/or ultrasound. The introduction element is preferentially an elongated hollow introduction element like a catheter or needle, especially a brachytherapy catheter. The system is preferentially adapted to perform an HDR therapy, while the target region is heated and/or after the target region has been heated.

 In an embodiment the control unit is adapted to control the moving unit such
20 that the radiation source is moved to and stopped at a location within the subject, at which the determined temperature is larger than a predefined threshold temperature. Such a control of the movement of the radiation source within the introduction element depending on the determined temperature can lead to a further improved effectiveness of the application of the radiation to the target region.

25 Moreover, the system may comprise a target region providing unit for providing the position of the target region within the subject, wherein the temperature determination unit may be adapted to determine a temperature within the target region based on the temperature determined along the length of the introduction element and the provided target region and wherein the control unit may be adapted to control the moving unit such
30 that the radiation source is not introduced into the subject or retracted from the subject, if the determined temperature within the target region is below a predefined threshold temperature. In particular, therapy delivery may be stopped, if the target region is not in hyperthermia. The determined temperature within the target region may be, for instance, an average of the temperatures along the length of the introduction element, which are within the target region,

a minimum of these temperatures, a maximum of these temperatures, et cetera. In an embodiment the control unit may be adapted to control the moving unit such that the radiation source is not introduced into the subject or retracted from the subject, if a single, a predefined amount or all of the temperatures along the length of the introduction element, which are within the target region, are below the predefined threshold temperature.

Furthermore, the system may comprise an output unit for outputting an alarm, if the determined temperature within the target region is below a predefined threshold temperature, i.e., for instance, an alarm may be generated, if the target region is not in hyperthermia. The user may then stop the application of the radiation to the target region by removing the radiation source from the subject, thereby ensuring that the radiation is applied to the subject, especially the target region, only if the radiation is very effective.

In an embodiment the system comprises a target region providing unit for providing the position of the target region within the subject and a plan generation unit for generating a plan defining dwell positions and dwell times of the radiation source within the subject based on the provided position of the target region within the subject and the determined temperature, wherein the control unit is adapted to control the moving unit in accordance with the generated plan. The generation of the plan can also include an adaptation of an existing plan. The adaptation may be performed even during therapy delivery. The plan generation unit may be adapted to generate the plan such that it defines dwell positions only at locations within the subject, at which the determined temperature is larger than a predefined threshold temperature. Moreover, the plan generation unit may be adapted to generate the plan such that a dwell time at a dwell position depends on the temperature at the dwell position. For instance, if at a location within the target region the temperature is higher than a threshold temperature such that an increased oxygen level can be assumed, but if the temperature is still relatively low, the dwell time may be larger, whereas, if the temperature is larger, the dwell time may be smaller at this location. Generating the plan not only depending on, for instance, the position of the target region, but also on the current temperature distribution within the target region, can further improve the effectiveness of the application of the radiation to the target region.

In a preferred embodiment the introduction element comprises an optical fiber arranged along the length of the introduction element for generating optical signals which are indicative of the temperature along the length of the introduction element, wherein the temperature determination unit is adapted to determine the temperature along the length of the introduction element based on the generated optical signals. The optical fiber

preferentially comprises Bragg gratings for generating the optical signals. Alternatively or in addition, the temperature determination unit can be adapted to determine the temperature along the introduction element in another way. For instance, an image based temperature measuring technique can be used for determining the temperature along the length of the introduction element. In particular, a magnetic resonance or ultrasound thermometry technique may be used for determining the temperature along the length of the catheter. In an embodiment the position of the introduction element in an image is determined by segmentation and the temperature along the length of the introduction element is determined based on the image values at the determined position of the introduction element.

The system may further comprise a position determination unit for determining the position of the introduction element, especially based on the optical signals. Moreover, the plan generation unit may be adapted to generate a plan defining dwell positions and dwell times of the radiation source within the subject based on a provided position of the target region within the subject, the determined temperature and the determined position of the introduction element, wherein the control unit may be adapted to control the moving unit in accordance with the generated plan. Determining the position of the introduction element based on the optical signals, especially based on generated optical shape sensing signals, allows for a very accurate determination of the position of the introduction element within the subject, wherein this very accurately determined position can be used, in order to initially generate or adapt a plan defining dwell positions and dwell times of the radiation source, especially in real-time. This can lead to a further increased effectiveness of the application of the radiation to the target region. However, the position determination unit can also be adapted to determine the position of the introduction element in another way, for instance, by using an electromagnetic tracking technique, an ultrasound tracking technique, et cetera.

In an embodiment the system comprises an image providing unit for providing an image of the subject showing at least the target region, and an output unit comprising a display for displaying the image overlaid with a representation of the introduction element based on the determined position of the introduction element. This allows a user to check whether the introduction element is at a desired position within the subject.

The target region providing unit may be adapted to determine the position of the target region based on the provided image of the subject. For instance, the target region providing unit may be adapted to segment the target region in the provided image, in order to determine the position of the target region.

The output unit may be adapted to output a single value depending on the determined temperature. The single value may be a minimum value, a maximum value or an average value, especially within the target region. Moreover, the system may comprise several introduction elements for being inserted into the subject and for introducing a radiation source into the subject, wherein the temperature may be determined along the lengths of the introduction elements by using, for instance, optical fibers arranged along the lengths of the introduction elements, in order to determine a three-dimensional temperature distribution within the subject based on the optical signals.

In an embodiment the system comprises an image providing unit for providing an image of the subject showing at least the target region, wherein the temperature determination unit is adapted to determine a first temperature along the length of the introduction element based on the optical signals and to determine a second temperature based on the provided image by using an image-to-temperature transformation process, wherein the image-to-temperature transformation process is calibrated by using the first temperature. The image providing unit may include an ultrasound imaging device or magnetic resonance imaging device. Thus, the temperature, which is obtained based on, for instance, the optical signals, can be used to calibrate another, image-based temperature measurement procedure, wherein, after this calibration has been performed, the temperature obtained from the image-based temperature measuring procedure can be used for determining the temperature within, for example, the target region. This additional temperature information can be, for instance, shown on a display and/or used by the control unit for controlling the moving unit, which may lead to a further improved effectiveness of applying the radiation to the target region. In particular, the temperature determined along the length of the introduction element may directly be used for controlling the moving unit and/or the temperature determined along the length of the introduction element may indirectly be used for controlling the moving unit, wherein in the latter case the temperature along the length of the introduction element may be used for calibrating the image-to-temperature transformation and a temperature, for instance, within the target region, may be determined based on the calibrated image-to-temperature transformation.

The temperature determination unit may be adapted to determine the temperature along the entire length of the introduction element or along a part of the length of the introduction element. In the latter case the temperature may be determined along a part of the length of the introduction element which is arranged within the target region.

The system preferentially further comprises a control unit for controlling the heating unit depending on the determined temperature. For instance, the heating unit can be controlled such that the target region, especially the entire target region, has a temperature being larger than a predefined threshold temperature, in order to ensure that the target region is in a hyperthermia condition, when placing the radiation source within or close to the target region. This can lead to a further improved effectiveness of applying the radiation to the target region.

In a further aspect of the present invention a method for applying radiation to a target region within a subject is presented, wherein the method comprises:

- heating the target region by using a heating unit,
- determining a temperature along a length of an elongated introduction element, which has been inserted into the subject for introducing a radiation source emitting radiation to be applied to the target region into the subject, by a temperature determination unit, and
- controlling a moving unit for moving the radiation source within the introduction element such that the radiation source is located within or close to the target region depending on the determined temperature by a control unit.

In a further aspect of the present invention a computer program for applying radiation to a target region within a subject is presented, wherein the computer program comprises program code means for causing a system as defined in claim 1 to carry out the steps of the method as defined in claim 14, when the computer program is run on a computer controlling the system.

It shall be understood that the system of claim 1, the method of claim 14 and the computer program of claim 15 have similar and/or identical preferred embodiments, in particular, as defined in the dependent claims.

It shall be understood that a preferred embodiment of the present invention can also be any combination of the dependent claims or above embodiments with the respective independent claim.

These and other aspects of the invention will be apparent from and elucidated with reference to the embodiments described hereinafter.

BRIEF DESCRIPTION OF THE DRAWINGS

In the following drawings:

Fig. 1 shows schematically and exemplarily an embodiment of a system for applying radiation to a target region within a subject,

Fig. 2 shows schematically and exemplarily introduction elements of the system to be inserted into the subject for applying the radiation to the target region,

5 Fig. 3 illustrates schematically and exemplarily a possible arrangement of the introduction elements after having been inserted into the subject,

Fig. 4 shows schematically and exemplarily a sectional view of an introduction element,

10 Fig. 5 shows schematically and exemplarily a visualization of temperatures determined at different locations along a length of an introduction element, and

Fig. 6 shows a flowchart exemplarily illustrating an embodiment of a method for applying radiation to a target region within a subject.

DETAILED DESCRIPTION OF EMBODIMENTS

15 Fig. 1 shows schematically and exemplarily a system for applying radiation to a target region within a subject. In this embodiment the system 1 is a brachytherapy system for applying a brachytherapy to a subject 2 lying on a support means 3 like a table. The brachytherapy system 1 comprises a placing unit 5 for placing a radiation source close to or within a target region within the subject 2 for directing radiation emitted by the radiation
20 source to the target region. The radiation source 10 is preferentially a radioactive radiation source emitting radioactive radiation like Ir-192. The placing unit 5 is exemplarily and schematically shown in more detail in Fig. 2.

The placing unit 5 comprises several elongated introduction elements 12, which in this embodiment are catheters, with tips 20 for being introduced into the subject 2.
25 The placing unit 5 further comprises a drive wire 13 to which the radiation source 10 is attached, wherein the drive wire 13 with the radiation source 10 can be moved within each of the catheters 12 for placing the radiation source 10 at desired dwell positions for desired dwell times. The placing unit 5 further comprises a moving unit 14, which may also be regarded as being an afterloader and which is adapted to introduce the radiation source 10
30 into and to move the radiation source 10 within the different catheters 12 by using a motor. In particular, the moving unit 14 may be adapted to drive the radiation source 10 through an indexer that connects with the different catheters 12. For more details regarding this kind of placing the radiation source 10 within the subject reference is made to the “A Practical Guide to Quality Control of Brachytherapy Equipment” edited by J. Venselaar and J. Perez-

Calatayud, European Society for Therapeutic Radiology and Oncology (2004), which is herewith incorporated by reference.

The placing unit can comprise further elements for assisting in placing the radiation source at the desired dwell positions for the desired dwell times within the subject

2. For instance, the placing unit can comprise a template which can be used for inserting the catheters in a more uniform configuration into the subject 2.

In this embodiment the system 1 is adapted to treat a target region, which is preferentially a tumor region, in a prostate. The radiation source may be placed within the target region and/or close to the target region, i.e., in particular, adjacent to the target region.

Fig. 3 shows schematically and exemplarily a possible arrangement of the catheters 12 of the placing unit 5 within the prostate 11.

Each catheter 12 comprises an optical fiber with Bragg gratings. In particular, as schematically and exemplarily shown in Fig. 4, each catheter 12 may comprise three optical fibers 17 with Bragg gratings within an outer wall 16, wherein these three optical fibers 17 may be angularly equidistantly distributed, i.e. they may have an angular distance to each other of 120 degrees. The system 1 further comprises an optical sensing control unit 9 for generating optical signals, which are indicative of the temperature along the respective catheter 12 and the position of the respective catheter 12 within the subject, by using the optical fibers 17 with the Bragg gratings.

For instance, each optical fiber 17 may comprise ten Bragg gratings with a length of 8 mm and separated by a distance of 20 mm along the respective optical fiber 17. The optical fibers 17 may be connected to a broadband source and a detector of the optical sensing control unit 9. The peak reflected wavelength for each Bragg grating shifts due to changes in strain and temperature such that these shifts can be used to reconstruct the shape of and temperature along the respective catheter 12. In particular, the shape of the entire respective catheter 12 relative to a respective known anchoring location can be reconstructed, in order to determine the position of each portion or section of the respective catheter 12, and the temperature at different portions or sections along the length of the respective catheter 12 can be determined. For example, the shift $\Delta\lambda_B$ of a peak reflected wavelength λ_B depending on a strain ε and a temperature change ΔT can be given by

$$\frac{\Delta\lambda_B}{\lambda_B} = k_s \varepsilon + k_T \Delta T, \quad (1)$$

wherein k_s and k_T denote constants, which can be determined by calibration measurements, and wherein this equation can be used together with the knowledge that the three optical fibers 17 of a same catheter 12 have an angular distance of 120 degrees to each other for determining the shape of the respective catheter 12 and the temperature along the length of the respective catheter 12. The temperature between the different portions or sections, at which the temperature has been determined, may be determined by interpolation. For more details regarding the determination of the shape and hence position of the respective catheter 12 and of the temperature along the length of the respective catheter 12 based on the optical signals reference is made to, for instance, "Fiber Optic Sensors" by F. T. S. Yu et al., Marcel Dekker Inc., (2002), especially chapter 4 of this book, which is herewith incorporated by reference. The determination of the temperature along the length of the respective catheter 12 is performed by a temperature determination unit 13 and the shape and hence the position of the respective catheter 12 is determined by a position determination unit 35.

The system 1 further comprises an imaging unit 4, 8 being, in this embodiment, an ultrasound unit. The ultrasound unit comprises an ultrasound probe 4 and an ultrasound control unit 8. The ultrasound probe 4 may be placed on the outside surface of the subject 2 as schematically and exemplarily illustrated in Fig. 1, or the ultrasound probe may be arranged within the subject 2, in order to generate an image of the subject 2, especially of the target region. For instance, the ultrasound probe may be a transrectal ultrasound probe. The generated image can be shown to a user on a display 41, in order to guide the user while introducing the catheters 12 into the subject 2. In another embodiment the imaging unit can be another kind of imaging device like a magnetic resonance imaging device. Since the imaging unit 4, 8 provides the image showing the subject 2 including the target region, the imaging unit 4, 8 can be regarded as being an image providing unit.

In an embodiment the positions of the catheters 12 within the subject 2 determined by the position determination unit 35 can be registered with the image of the subject provided by the imaging unit 4, 8, in order to allow the display 41 to show representations of the catheters 12 within the image based on the determined positions of the catheters 12. Moreover, a target region providing unit 32 can be adapted to determine the position of the target region within the subject 2 based on the image provided by the imaging unit 4, 8, for instance, by segmenting the target region within the provided image. Based on the determined position of the target region within the subject 2, a representation of this target region may be shown on the display 41. In this way the display 41 can guide the user while introducing the catheters 12 into the subject 2.

Instead of or in addition to generating a current image of the subject 2, the imaging unit can be adapted to provide a pre-interventional image, wherein also in this case the determined positions of the catheters 12 within the subject 2 can be registered with the image of the subject 2 provided by the imaging unit, in order to allow the display 41 to show a representation of the catheters 12 overlaid with the provided image. For registering the determined positions of the catheters 12 with the provided image known registration techniques can be used, which may be based on detecting a catheter equipped with an optical fiber with Bragg gratings in an image generated by the imaging unit, while the position of the catheter is determined based on the optical signals.

The system 1 further comprises a heating unit 30 for heating the target region. For instance, the heating unit may be adapted to heat the target region by using an ultrasound technique, a microwave technique or a radiofrequency technique. In particular, the heating unit may be adapted to perform a transurethral microwave heating or a high-intensity focused ultrasound (HIFU) heating, wherein ultrasound beams may be focused to a small focal zone, which may be located at the target region, by using a curved transducer or a phased array. For more details regarding the HIFU heating reference is made to, for instance, the article "HIFU for palliative treatment of pancreatic cancer" by T. Khokhlova and J. Hwang, volume 2, number 3, pages 175 to 184, Journal of Gastrointestinal Oncology (2011), which is herewith incorporated by reference. In an embodiment the ultrasound unit for generating ultrasound images may be integrated with an ultrasound-based heating unit. However, as schematically illustrated in Fig. 1, the ultrasound unit for generating ultrasound images and the ultrasound-based heating unit can also be separate units.

The system further comprises a brachytherapy control unit 15 for controlling the moving unit 14 depending on the determined temperature. The control unit 15 is preferentially further adapted to control the moving unit 14 depending on the provided position of the target region. In particular, the brachytherapy control unit 15 is adapted to control the moving unit 14 such that the radiation source 10 is moved to and stopped at a location within or close to, i.e. adjacent to, the target region, at which the determined temperature is larger than a predefined threshold temperature. This threshold temperature is preferentially predefined such that the target region is in a hyperthermia condition at the location within or close to the target region, in order to increase the effectiveness of applying the radiation to the target region. A location close to the target region is preferentially an adjacent or surrounding location which is close enough for allowing the radiation emitted by the radiation source to treat the target region.

The brachytherapy control unit 15 is preferentially adapted to control the moving unit 14 such that the radiation source 10 is not introduced into the subject 2 or retracted from the subject 2, if the temperature of the target region, which might be an average temperature of all temperatures measured within the target region, is below a predefined threshold temperature. This threshold temperature may be predefined such that, if the target region has a temperature being larger than the threshold temperature, the target region is in a hyperthermia condition. Moreover, in an embodiment the brachytherapy control unit 15 may be adapted to not introduce the radiation source into the subject 2 or to retract the radiation source 10 from the subject 2, if at each location within the target region, at which the temperature is measured, the temperature is below the predefined threshold temperature. As a threshold temperature 40 degree Celsius or a larger temperature may be used. In an embodiment the heating unit 30 may be controlled such that the target region should have a temperature within a range of 40 to 45 degree Celsius, wherein especially in this case the threshold temperature might be 40 degree Celsius.

Furthermore, the display 41 or another output unit like an acoustic output unit may be adapted to output an alarm, if among the temperatures determined within the target region at least one temperature is below a predefined threshold temperature and/or if the average temperature of the target region is below the predefined threshold temperature. Moreover, in an embodiment, if the radiation source is located at a certain dwell position within the subject 2, especially close to or within the target region, and if the temperature at this dwell position is smaller than the threshold temperature, the alarm may be output.

The brachytherapy control unit 15 may be adapted to control the moving unit 14 in accordance with a plan defining dwell positions and dwell times of the radiation source 10 within the subject 2, wherein this plan may have been generated by a plan generation unit 31. The plan generation unit 31 may be adapted to generate the plan based on the provided position of the target region, the determined temperature along the length of the catheters 12 and the determined positions of the catheters 12. The plan generation unit 31 may be adapted to initially generate the plan and/or to generate the plan by adapting an existing plan. In particular, the plan may be adapted in real-time based on a current temperature along the catheters 12 and/or current positions of the catheters 12 and/or a current position of the target region. The brachytherapy control unit 15 can be adapted to move the radiation source 10 in accordance with the real-time adapted plan defining optimized dwell positions and dwell times. The plan generation unit 31 can be adapted to generate the plan such that it defines dwell positions only in regions within or close to the target region, in which the determined

temperature is larger than the predefined threshold temperature. Moreover, the plan generation unit 31 can be adapted to generate the plan such that a dwell time at a dwell position depends on the temperature at the dwell position. Generally, the plan generation unit 31 can comprise plan generation rules defining dwell positions and dwell times depending on the position of the target region, the positions of the catheters and the temperature along the catheters.

The system 1 further comprises a heating control unit 34 for controlling the heating unit 30 depending on the determined temperature. For instance, the control unit 34 may control the heating unit 30 such that at least at dwell positions defined by the plan generated by the plan generation unit the temperature is larger than the predefined threshold temperature. In particular, the heating control unit 34 can be adapted to control the heating unit 30 such that all temperatures determined along the catheters 12, which have been determined for locations being within the target region, are larger than the predefined threshold temperature.

The system 1 further comprises an input unit 40 like a keyboard, a computer mouse, a touch pad, et cetera, in order to allow the user to, for instance, input commands into the system 1 like a start command for starting a brachytherapy procedure, a stop command for stopping a brachytherapy procedure, et cetera. The input unit 40 may also be used to input parameters defining the brachytherapy procedure like dwell positions and dwell times.

The display 41 may be adapted to display a single temperature value for the entire target region. For instance, a minimum temperature value, a maximum temperature value or an average temperature value may be determined for the target region based on all temperatures determined for locations along the catheters 12, which are within the target region, and the minimum temperature value, the maximum temperature value or the average temperature value may be shown on the display 41. However, it is of course also possible that, for instance, a chart showing the temperature values along the length of a catheter is displayed as schematically and exemplarily illustrated in Fig. 5. Fig. 5 shows a relative temperature T in Kelvin for different locations z in arbitrary units along a catheter. The z locations schematically and exemplarily illustrated in Fig. 5 correspond to different locations of Bragg gratings along the respective catheter. Temperature values for locations in between the locations shown in Fig. 5 can be determined by, for instance, interpolation. The temperatures determined for the locations, at which the Bragg sensors, i.e. the Bragg gratings, are present and the interpolated temperatures for intermediate locations can be used, for instance, by the plan generation unit 31 for generating a plan defining dwell positions and

dwelling times, wherein the brachytherapy control unit 15 may control the moving unit 14 in accordance with the plan, in order to indirectly, i.e. via the plan, control the moving unit 14 depending on the temperatures, and/or the temperatures may be directly used by the brachytherapy control unit 15 for controlling the moving unit for moving the radiation source within the catheters depending on the temperatures along the lengths of the catheters and/or the temperature may be used by the heating control unit 34 for controlling the heating unit 30 depending on the temperatures along the lengths of the catheters. Also a two-dimensional or a three-dimensional temperature map may be determined based on the temperatures along the lengths of the different catheters.

The temperature determination unit 13 can be adapted to use the temperature determined along the lengths of the catheters 12 for calibrating an image-to-temperature transformation process, which may be applied to an image generated by the imaging unit 4, 8. For instance, the imaging unit 4, 8 can be adapted to use ultrasound thermometry, wherein an ultrasound image is transformed into a temperature distribution. This ultrasound thermometry technique can be calibrated by determining the temperature of the subject by using ultrasound thermometry, while the temperature is known from the optical-signals-based temperature determination. In another embodiment also another image-based temperature determination technique like a magnetic-resonance-image-based temperature determination technique can be calibrated by using the temperatures determined along the catheters based on the optical signals. The temperatures determined by the calibrated image-based temperature determination techniques may then also be shown on the display 41 and used by the plan generation unit 31, the brachytherapy control unit 15 and/or the heating control unit 34. In the following an embodiment of a method for applying radiation to a target region within a subject will exemplarily be described with reference to a flowchart shown in Fig. 6.

After the catheters 12 have been inserted into the subject 2 such that they are close to or within the target region and before or during introducing the radiation source 10 through a catheter 12 into the subject 2 such that it is located close to or within the target region, in step 101 the target region is heated by using the heating unit 30. In step 102 optical signals are generated, which are indicative of the temperature along the lengths of the catheters 12, by using the optical fibers 17 arranged along the lengths of the catheters 12, wherein in step 103 the temperature along the lengths of catheters 12 is determined based on the optical signals by the temperature determination unit 13. In step 104 the moving unit 14 is controlled by the brachytherapy control unit 15 depending on the determined temperature such that the radiation source 10 is moved to a location within or close to the target region.

At least steps 102 to 104 may be carried out in a loop such that the temperature is continuously measured and the movement of the radiation source within the catheters is controlled depending on the currently present temperature, i.e. temperature distribution, along the lengths of the catheters.

5 Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures, i.e., for instance, to temperatures within a range of 40 to 45 degrees Celsius, in order to damage and kill cancer cells. Hyperthermia can be applied to a relatively small area such as a tumor region, wherein a technique may be used, which delivers energy to heat the tumor region like a microwave technique, a radiofrequency technique or an
10 ultrasound technique. Radiation therapy is another type of cancer treatment, in which ionizing radiation is used to control or kill malignant cells. The ionizing radiation can be administered using external beam radiation therapy (EBRT), permanent interstitial sources (low dose rate brachytherapy) or temporary interstitial sources (HDR brachytherapy).

Hyperthermia and radiation therapy complement each other. Ionizing radiation
15 destroys cancerous tissue primarily through the generation of oxygen radicals that attack the tumor DNA. Thus, tumor cells containing an insufficient oxygen level are relatively resistant to ionizing radiation. A radiation therapy is more effective in well-oxygenated tumors such that hyperthermia, which leads to an improved blood circulation and hence to an improved oxygen supply, improves the effectiveness of the radiation therapy. In addition, hyperthermia
20 can also cause an accumulation of proteins in the cell nucleus, thereby preventing a self-repair of cancer cell DNA. Finally, ionizing radiation and hyperthermia damage cells during different phases of the cell cycle. During the synthesis phases, tumor cells are resistant to ionizing radiation, but susceptible to the destructive effects of hyperthermia. Combining hyperthermia and radiation therapy can therefore improve a cancer therapy. In particular,
25 hyperthermia can be regarded as being a very effective potentiator of radiation therapy.

The system described above with reference to Figs. 1 to 5 is adapted to monitor the temperature in the target region, especially in tumor tissue, during radiation therapy. Showing the determined temperatures on the display, i.e. reporting the temperature measured along the catheters to a clinical user, provides a quality assurance for the
30 combination therapy. However, the monitored temperature can also be used to provide a temperature-based adaptation and/or generation of radiation therapy plans, especially as described above. In particular, the temperature measurements may be used as an input for planning a radiation therapy, in order to confine the treatment only to susceptible areas and/or to adapt the radiation dose, i.e. the dwell times, based on the respective local temperature.

The radiation source, which is preferentially a highly radioactive source and which is preferentially used to perform an HDR brachytherapy, traverses the catheters positioned in and/or around the target region, in order to deliver ionizing radiation. Dedicated temperature sensing needles or catheters would either be positioned too far from the target region and/or block potential locations for treatment delivery catheters. The temperature sensing functionality is therefore preferentially integrated in the catheters. Moreover, the temperature sensing in the catheters is preferentially combined with tracking/navigation technology, for instance, by using an optical shape sensing technology as described above.

The system can be adapted to raise an alarm, if the target region is no longer in hyperthermia, wherein the alarm may be a visible alarm, an audible alarm, a tactile alarm, et cetera. Moreover, the system can be adapted to stop therapy delivery, if the target region is no longer in hyperthermia. Furthermore, based on the measured temperature in the target region the system may modify the therapy delivery. For instance, the moving unit, which may be regarded as being an afterloader, can be instructed by the brachytherapy control unit to shorten or lengthen dwell times at certain dwell positions based on the measured temperature. This adaptation of the therapy delivery can be an automatic procedure. Moreover, also an interactive procedure can be provided, in which the user is informed about the temperature in the target region, whereupon the user may modify the therapy delivery, especially a radiation therapy plan defining dwell positions and dwell times, based on the information about the temperature in the target region. For instance, based on the temperature in the target region, the user can be allowed to decide on a continuation of the treatment, i.e. of the heating of the target region and/or the introduction of the radiation source into or close to the target region. This may prevent unnecessary pain which may be induced by, for instance, temperature elevation.

Although in above described embodiments the optical fibers of the catheters comprise discrete Bragg gratings, which are used for generating optical signals, which in turn are used to reconstruct the shape and hence the position of the respective catheter and to determine the temperature along the length of the respective catheter, in other embodiments instead of using optical fibers with discrete Bragg gratings alternative fiber optic approaches may be used like the use of continuous gratings.

Although in above described embodiments the introduction element is a catheter, in other embodiments the introduction element can also be another introduction element for being introduced into the subject. Moreover, although in above described

embodiments several introduction elements have been inserted into the subject, in other embodiments only a single introduction element may be inserted into the subject.

Other variations to the disclosed embodiments can be understood and effected by those skilled in the art in practicing the claimed invention, from a study of the drawings, the disclosure, and the appended claims.

In the claims, the word "comprising" does not exclude other elements or steps, and the indefinite article "a" or "an" does not exclude a plurality.

A single unit or device may fulfill the functions of several items recited in the claims. The mere fact that certain measures are recited in mutually different dependent claims does not indicate that a combination of these measures cannot be used to advantage.

Operations like the determination of a temperature along an introduction element, the determination of a position of an introduction element, the determination of a target region within a subject, the generation of a plan defining dwell positions and dwell times, et cetera and/or the control of the system for applying radiation to a target region within a subject, which have been described as being performed by a certain number of units or devices, can be performed by any other number of units or devices. For instance, the determination of the temperature along the introduction element, the determination of the position of the introduction element within the subject, the determination of the position of the target region within the subject, the generation of the plan defining dwell positions and dwell times and other procedures can be performed by a single processing unit. These operations and/or the control of the system for applying radiation to a target region within a subject in accordance with the method for applying radiation to a target region within a subject can be implemented as program code means of a computer program and/or as dedicated hardware.

A computer program may be stored/distributed on a suitable medium, such as an optical storage medium or a solid-state medium, supplied together with or as part of other hardware, but may also be distributed in other forms, such as via the Internet or other wired or wireless telecommunication systems.

Any reference signs in the claims should not be construed as limiting the scope.

The invention relates to a system for applying radiation to a target region within a subject. An introduction element like a brachytherapy catheter is inserted into the subject and a radiation source is moved within the introduction element such that it is located within or close to the target region. The target region is heated, wherein the movement of the

radiation source within the introduction element is controlled depending on the temperature along the introduction element. The susceptibility of the subject for the radiation emitted by the radiation source at a respective location along the length of the introduction element can depend on the temperature at the respective location such that by controlling the movement
5 of the radiation source depending on the temperature along the length of the introduction element the application of the radiation can be optimized.

CLAIMS:

1. A system for applying radiation to a target region within a subject, wherein the system (1) comprises:

- an elongated introduction element (12) for being inserted into the subject (2) and for introducing a radiation source (10) emitting radiation to be applied to the target

5 region into the subject (2),

- a moving unit (14) for moving the radiation source (10) within the introduction element (12) such that the radiation source (10) is located within or close to the target region,

- a heating unit (30) for heating the target region,

10 - a temperature determination unit (13) for determining the temperature along the length of the introduction element (12), and

- a control unit (15) for controlling the moving unit (14) depending on the determined temperature.

15 2. The system as defined in claim 1, wherein the control unit (15) is adapted to control the moving unit (14) such that the radiation source (10) is moved to and stopped at a location within the subject (2), at which the determined temperature is larger than a predefined threshold temperature.

20 3. The system as defined in claim 1, wherein the system (1) further comprises a target region providing unit (32) for providing the position of the target region within the subject (2), wherein the temperature determination unit (13) is adapted to determine a temperature within the target region based on the temperature determined along the length of the introduction element (12) and the provided target region and wherein the control unit (15)

25 is adapted to control the moving unit (14) such that the radiation source (10) is not introduced into the subject (2) or retracted from the subject (2), if the temperature within the target region is below a predefined threshold temperature.

4. The system as defined in claim 1, wherein the system (1) further comprises a target region providing unit (32) for providing the position of the target region within the subject (2), wherein the temperature determination unit (13) is adapted to determine a temperature within the target region based on the temperature determined along the length of the introduction element (12) and the provided target region, wherein the system (1) further comprises an output unit (41) for outputting an alarm, if the temperature within the target region is below a predefined threshold.

5. The system as defined in claim 1, wherein the system (1) further comprises a target region providing unit (32) for providing the position of the target region within the subject (2) and a plan generation unit (31) for generating a plan defining dwell positions and dwell times of the radiation source (10) within the subject (2) based on the provided position of the target region within the subject (2) and the determined temperature, wherein the control unit (15) is adapted to control the moving unit (14) in accordance with the generated plan.

6. The system as defined in claim 5, wherein the plan generation unit (31) is adapted to generate the plan such that it defines dwell positions only at locations within the subject (2), at which the determined temperature is larger than a predefined threshold temperature.

7. The system as defined in claim 5, wherein the plan generation unit (31) is adapted to generate the plan such that a dwell time at a dwell position depends on the temperature at the dwell position.

8. The system as defined in claim 1, wherein the introduction element (12) comprises an optical fiber (17) arranged along the length of the introduction element (12) for generating optical signals, which are indicative of the temperature along the length of the introduction element (12) and wherein the temperature determination unit (13) is adapted to determine the temperature along the length of the introduction element (12) based on the generated optical signals.

9. The system as defined in claim 8, wherein the system (1) further comprises a position determination unit (35) for determining the position of the introduction element (12) based on the optical signals.

5 10. The system as defined in claim 8, wherein the system (1) comprises an image providing unit (4, 8) for providing an image of the subject (2) showing at least the target region, wherein the temperature determination unit (13) is adapted to determine a first temperature along the length of the introduction element (12) based on the optical signals and to determine a second temperature based on the provided image by using an image-to-
10 temperature transformation process, wherein the image-to-temperature transformation process is calibrated by using the first temperature.

11. The system as defined in claim 1, wherein the system (1) further comprises a position determination unit (35) for determining the position of the introduction element (12),
15 a target region providing unit (32) for providing the position of the target region within the subject (2) and a plan generation unit (31) for generating a plan defining dwell positions and dwell times of the radiation source (10) within the subject (2) based on the provided position of the target region within the subject (2), the determined temperature and the determined position of the introduction element (12), wherein the control unit (15) is adapted to control
20 the moving unit (14) in accordance with the generated plan.

12. The system as defined in claim 1, wherein the system (1) further comprises a position determination unit (35) for determining the position of the introduction element (12), an image providing unit (4, 8) for providing an image of the subject (2) showing at least the
25 target region and an output unit (41) comprising a display for displaying the image overlaid with a representation of the introduction element (12) based on the determined position of the introduction element (12).

13. The system as defined in claim 1, wherein the system (1) further comprises a
30 control unit (34) for controlling the heating unit (30) depending on the determined temperature.

14. A method for applying radiation to a target region within a subject (2), wherein the method comprises:

- heating the target region by using a heating unit (30),
- determining a temperature along a length of an elongated introduction element (12), which has been inserted into the subject (2) for introducing a radiation source (10) emitting radiation to be applied to the target region into the subject (2), by a temperature determination unit (13), and
- controlling a moving unit (14) for moving the radiation source (10) within the introduction element (12) such that the radiation source (10) is located within or close to the target region depending on the determined temperature by a control unit (15).

10 15. A computer program for applying radiation to a target region within a subject (2), the computer program comprising program code means for causing a system as defined in claim 1 to carry out the steps of the method as defined in claim 14, when the computer program is run on a computer controlling the system.

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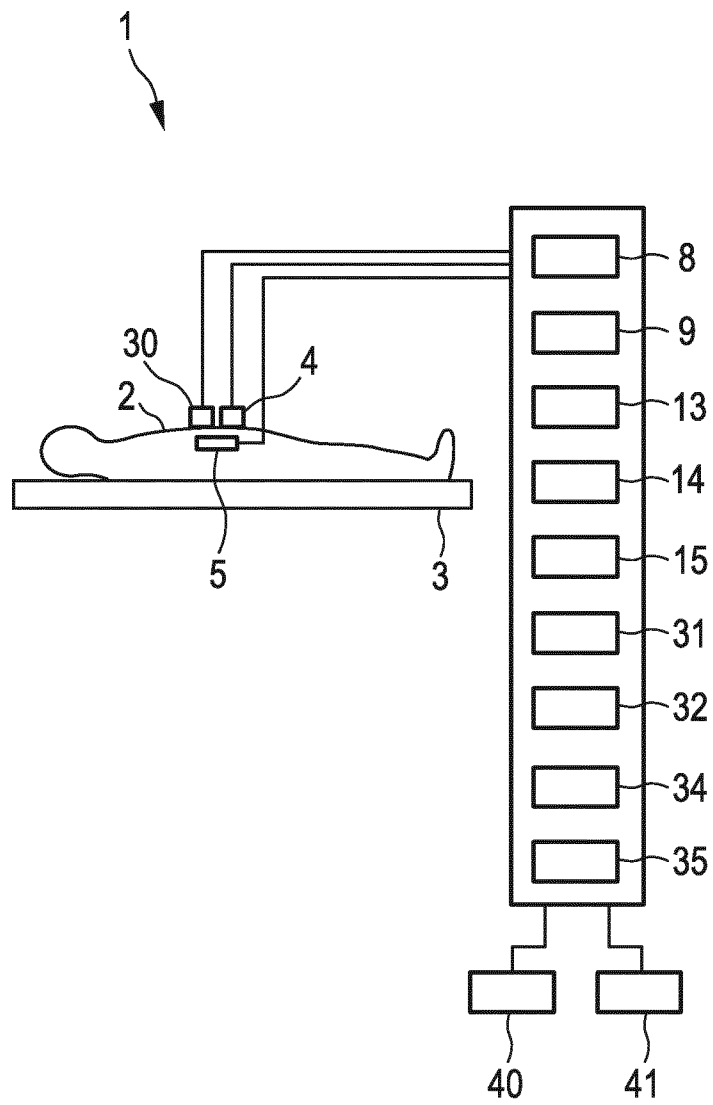


FIG. 1

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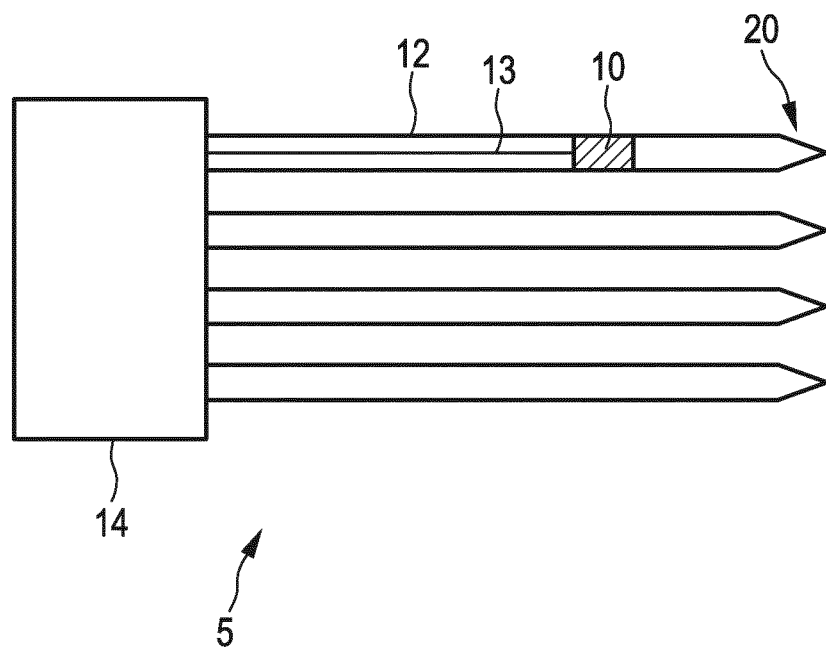


FIG. 2

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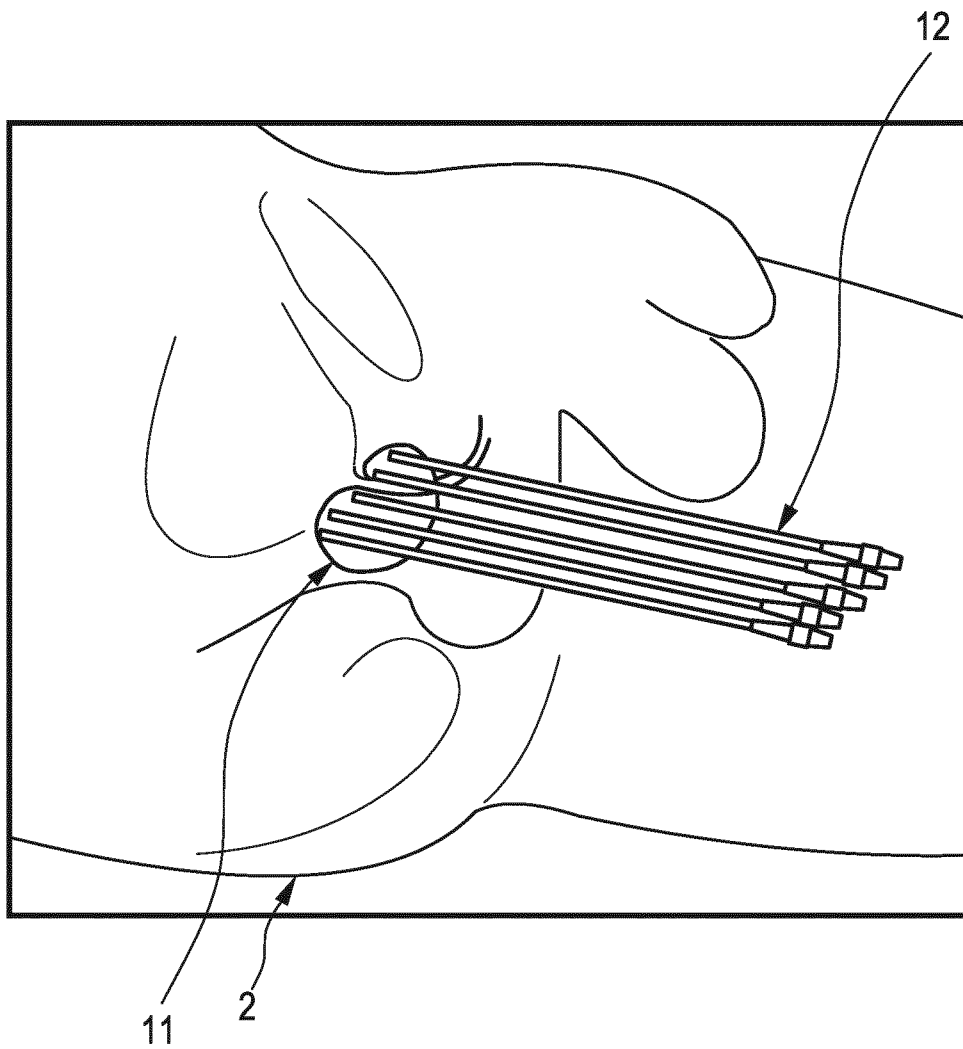


FIG. 3

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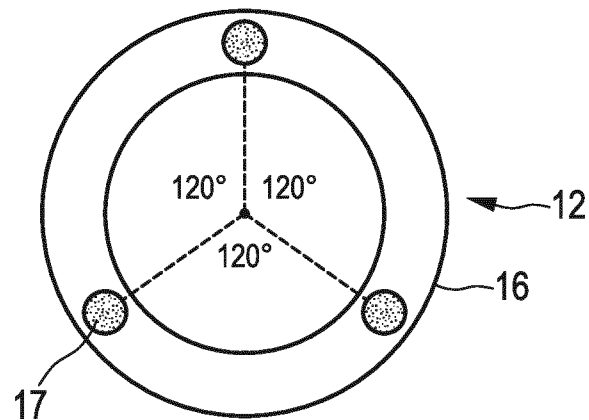


FIG. 4

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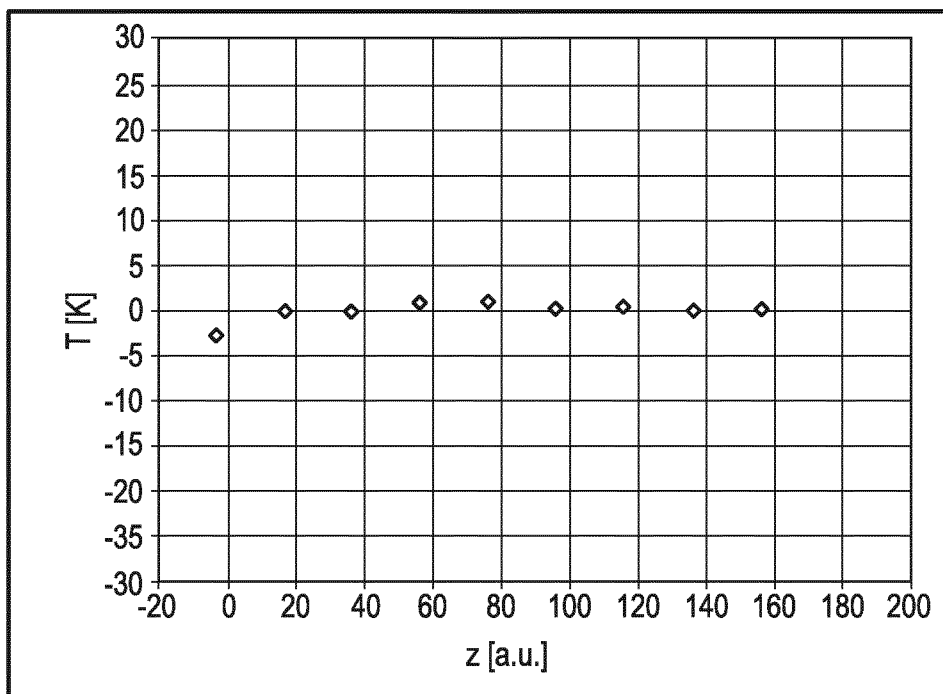


FIG. 5

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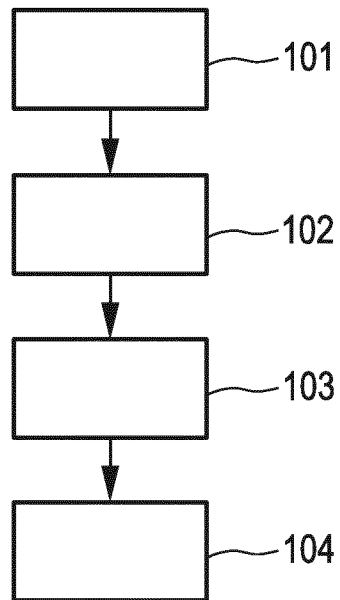


FIG. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2015/053962

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: **14**
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy and surgery
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/053962

A. CLASSIFICATION OF SUBJECT MATTER

INV. A61N5/10 A61N7/00 A61F7/00 A61N7/02
ADD. A61B19/00

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)

A61N A61F A61B

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)

EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>STEA B ET AL: "Interstitial thermoradiotherapy of brain tumors: Preliminary results of a phase I clinical trial", INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS, PERGAMON PRESS, USA, vol. 19, no. 6, 1 December 1990 (1990-12-01), pages 1463-1471, XP026847586, ISSN: 0360-3016 [retrieved on 1990-12-01] abstract; figures 1-3</p>	1-13,15
A	<p>DE 37 39 749 A1 (MUELLER CHRISTA DR [DE]) 8 June 1989 (1989-06-08) abstract; figure 1-</p>	1-13,15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

29 May 2015

Date of mailing of the international search report

09/06/2015

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Authorized officer

Kajzar, Anna

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2015/053962

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2009/094159 A1 (SENORX INC [US]; ACOSTA GEORGE M [US]; LUBOCK PAUL [US]) 30 July 2009 (2009-07-30) paragraphs [0036], [0037], [0040]; figure 9 -----	1-13,15
A	KR 2010 0118177 A (KOREA ELECTROTECH RES INST [KR]) 5 November 2010 (2010-11-05) abstract; claims 1-3 -----	1-13,15
A	WANG Z ET AL: "Elimination of dose-rate effects by mild hyperthermia", INTERNATIONAL JOURNAL OF RADIATION: ONCOLOGY BIOLOGY PHYSICS, PERGAMON PRESS, USA, vol. 24, no. 5, 1 January 1992 (1992-01-01), pages 965-973, XP026846902, ISSN: 0360-3016 [retrieved on 1992-01-01] abstract; figure 1 -----	1-13,15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2015/053962

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 3739749	A1	08-06-1989	NONE

WO 2009094159	A1	30-07-2009	AU 2009206735 A1 30-07-2009
			CA 2712923 A1 30-07-2009
			CN 101959555 A 26-01-2011
			EP 2234668 A1 06-10-2010
			JP 2011509798 A 31-03-2011
			US 2009188098 A1 30-07-2009
			US 2009198095 A1 06-08-2009
			US 2013144105 A1 06-06-2013
			WO 2009094159 A1 30-07-2009

KR 20100118177	A	05-11-2010	NONE
