METHOD FOR THERAPEUTIC ADMINISTRATION OF RADIONUCLEOSIDES

Inventors: William D. Dalke, Aurora, CO (US); Michael J. Gerber, Denver, CO (US); Kevin Lillehei, Englewood, CO (US); James E. Matsaura, Fort Collins, CO (US); Stephen L. Warren, Fort Collins, CO (US)

Assignee: Peak Biosciences Inc., Fort Collins, CO (US)

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ABSTRACT

Methods are provided for the local radiotherapy of cancers such as locally invasive, advanced stage solid tumors, and normal tissues penetrated by processes of cancerous tissue, through administration of Auger-electron emitting radionucleoside analogs using high-flow microinfusion techniques ("convection-enhanced delivery"). Direct infusion under pressure, at flow rates in excess of at least about 0.5 microliters/min of the radionucleosides provides for their mass transport through tissue to a much higher degree than could be achieved by passive, unpressurized diffusion. The unique properties of these radionucleoside analogs that provide for surprisingly efficacious delivery by high-flow microinfusion include rapid clearance from tissues following local injection without the benefit of sustained high-flow microinfusion, rapid and complete clearance via the blood stream, poor permeation of barriers such as the blood-brain barrier, and a highly potent, non-selective, but very short range killing effect on cells that are undergoing DNA replication that incorporate radionucleosides into their chromosomes.
METHOD FOR THERAPEUTIC ADMINISTRATION OF RADIONUCLEOSIDES

CLAIM OF PRIORITY TO RELATED APPLICATIONS

[0001] This application claims the priority of U.S. Patent Ser. No. 60/895,916, filed Mar. 20, 2007, which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Three major obstacles stand in the way of developing effective treatments for malignant solid tumors also known as cancers. First, recent studies have revealed an unanticipated degree of genetic heterogeneity among cancers. Even cancers arising in the same tissue and having indistinguishable microscopic features, i.e., solid tumors in the same pathological class, may be genetically and metabolically heterogeneous. This has been demonstrated for numerous pathological tumor types arising in tissues throughout the body, including malignant gliomas (e.g., glioblastoma multiforme) that arise in the central nervous system. Thus, “cancer” is a collection of literally hundreds of genetically distinct diseases, each with a different metabolic profile, and thus a different set of potential therapeutic targets. In view of such a striking degree of tumor heterogeneity, biochemical targeting, i.e. the search for agents that specifically target each tumor’s particular metabolic profile, is a daunting challenge.

[0003] Second, most currently available anticancer drugs, including cytotoxic agents and the so-called “targeted” agents, lack direct and definitive cell killing mechanisms. Most anticancer agents block enzymes, receptors or growth factors, and in doing so, alter the metabolism and/or signal transduction pathways in the cancer cells. As a result of such perturbations, the cancer cells are prompted to undergo programmed cell death (also known as “apoptosis”). However, a small subset of the cancer cells can often tolerate, evade or bypass the effects of such compounds on signal transduction and metabolism. The resistant subset of cancer cells continues to grow, even in the presence of the targeted agent, and as a result, the entire tumor eventually becomes resistant to the effects of the drug.

[0004] While many excellent targeted therapeutic agents have been developed to control blood pressure or to dampen the effects of inflammation, target-based drug discovery has not yet provided a failsafe mechanism to eliminate genetically and metabolically heterogeneous malignant solid tumors. Indeed, it is possible that a robust and “druggable” target may not exist in many types of cancers.

[0005] Radiotherapy, also known as ionizing radiation or x-ray therapy, is another commonly used treatment for malignant solid tumors. Ionizing radiation is curative for many early stage tumors, and is the treatment of choice to palliate or mitigate the symptoms of locally advanced cancers and selected metastatic cancers. Unfortunately, ionizing radiation damages the DNA of all cells in the treatment field, and thus lacks specificity for tumor cells. In addition, ionizing radiation has an inefficient cell killing mechanism. Cancer cells can repair the majority of their damaged DNA, thereby leading to re-growth of the tumor during intervals between radiation treatments. Resistance to the effects of ionizing radiation often occurs in clinical practice for a variety of reasons that are becoming increasingly well understood.

[0006] Third, the complete eradication of malignant solid tumors requires elimination of the cancer stem cells, a small subpopulation of the tumor cells believed to act as the “root” of many, if not all, malignant tumors. In most tumors examined, the cancer stem cells comprise less than 1% of the total tumor cell population, and yet these cells are responsible for maintaining the growth of the entire tumor by virtue of their capacity for self renewal and extended proliferation. Recent studies have shown that cancer stem cells are resistant to the effects of radiotherapy and drugs, and this is believed to contribute to the ability of many tumors to develop resistance to currently available treatments. Taken together, these three obstacles pose a big challenge to those searching for new “targeted” anticancer agents for solid tumors.

[0007] New and effective treatments based upon robust cancer cell killing mechanisms are needed to eliminate malignant tumor cells with a wide range of genetic and metabolic profiles and to eliminate the cancer stem cells, which are inherently resistant to chemotherapy and ionizing radiation. Optimal treatments would also minimize or completely avoid toxicity to normal cells. One approach to this problem is physically localized delivery of an agent capable of killing many different types of cancer cells, while at the same time having minimal or no toxicity to normal cells within the treatment field. This approach is distinct from the concept of targeted therapy, in which a different drug mechanism may be needed to treat each tumor according to its distinct genetic and metabolic profile.

[0008] The deficiencies of currently available cancer treatment modalities are especially glaring with respect to specific types of cancer, for example glioblastoma multiforme (GBM), a highly aggressive type of cancer that constitutes the most common form of brain malignancy. Indeed, after nearly 35 years of investigations involving hundreds of experimental treatments and thousands of GBM patients participating in clinical trials, the prognosis of patients with newly diagnosed GBM is dismal. In a recent survey, the survival following the diagnosis of GBM is only 42% at 6 months, 18% at one year, and 3% at 2 years.

[0009] A unique cell killing mechanism that has garnered considerable interest is the use of Auger electrons. These electrons are emitted by radionuclides that decay by electron capture and internal conversion. Examples of Auger emitting radionuclides include \(^{123}I\), \(^{124}I\), \(^{125}I\), \(^{77}Br\) and \(^{80}Br\). Another Auger electron emitting radionuclide is \(^{211}At\). Auger electrons have energies even lower than the energy of the beta particle emitted by tritium. This effect is amplified, because some Auger emitters release multiple electrons with each nuclear transformation. The low energy of the Auger electrons results in extremely short particle path lengths within tissues, which is highly desirable, because it minimizes collateral damage. Auger electrons travel only a few nanometers from the disintegrating atom from which they originate.

[0010] One molecular entity containing \(^{125}I\) is \(^{125}I\)-iodouridine-deoxyribonucleoside (\(^{125}I\)UDR), an analogue of thymidine. \(^{125}I\)UDR is recognized by DNA polymerase enzymes as a thymidine molecule, and thus is incorporated into the chromosomes at times of DNA synthesis. Once incorporated into the DNA, the Auger electrons, with their very short range, have direct access to the chemical backbone of the DNA double helix. When a DNA-bound \(^{125}I\) atom disintegrates, the Auger electrons cause irreparable destruction of the chromosomes within the target cell, but with minimal effect on cells in the immediate vicinity of the target cell.
Based upon this highly discriminating mechanism, $^{125}$IUDR and related compounds can destroy cells that make DNA, but have little or no effect on other cells. The type of chromosome destruction caused by $^{125}$IUDR appears to take place regardless of the particular genetic or metabolic abnormality driving the growth of a tumor cell. Thus, unlike currently available radiation treatments and anticaner drugs, $^{125}$IUDR has a direct, definitive and “broad spectrum” cell killing mechanism that is expected to be active against solid tumors with a wide range of genetic profiles. $^{125}$IUDR is exceptionally potent as indicated by its ability to destroy the chromosomes of replicating cancer cells at concentrations in the low picomolar range (e.g. 5 picomoles/liter). In fact, a single molecule of DNA-bound $^{125}$IUDR is capable of causing irreparable, lethal chromosome destruction. While cancer cells can repair the type of DNA damage caused by x-rays, and a variety of DNA-damaging drugs (e.g. cisplatin, busulfan, thiopeta, cyclophosphamide, carmustine, temozolomide, actinomycin-D, camptothecins, anthracylines, epipodophyllotoxins, nitrogen mustards, mitomycin C), there are no known mechanisms of resistance to the effects of $^{125}$IUDR.

[0011] A brief exposure to $^{125}$IUDR can kill a replicating cell; once a few molecules have been incorporated into the chromosome, the cell is destined to die regardless of whether it continues to be exposed to the $^{125}$IUDR. Thus, there is no need to maintain constant therapeutic levels of $^{125}$IUDR in the malignant tissues; multiple, repetitive exposures can kill the replicating cells exposed $^{125}$IUDR over the course of the treatment. By comparison, currently available agents usually need to be maintained continuously at therapeutic levels for a period of time, because such agents work by blocking enzymes, receptors and growth factors. If such agents are withdrawn, the blockade will cease and the cancer cells will recover and continue growing.

[0012] However, clinical studies of $^{125}$IUDR and related compounds, undertaken to determine whether the locally injected or intra-arterially infused radioactive nucleoside analogues are taken up by dividing cancer cells, showed that while human cancer cells rapidly incorporate $^{125}$IUDR into their chromosomes (DNA) following brief exposures to this agent, the compound is rapidly metabolized, inactivated and cleared from the circulation with a plasma half-life of less than 5 minutes in the human subjects. The rapid metabolism and clearance of $^{125}$IUDR and related compounds from the site of injection and from the bloodstream have precluded their use as locally or systemically administered anticancer agents.

[0013] Convection enhanced delivery (CED) is a technique whereby a solution containing a pharmacological agent is delivered under pressure to a tissue by means of an implanted catheter. For example U.S. Pat. No. 5,720,720 describes the technique of CED whereby the tip of an infusion catheter is positioned within cerebral tissues, and a solution is delivered through the catheter under pressure. At flow rates ranging between 0.5 and 15 $\mu$L/min in brain tissue, it was found that a solution can be delivered to target tissues up to a centimeter away from the point of pressure infusion. This contrasts with diffusion ranges of dissolved small molecules and macromolecules of no more than a few millimeters through tissue delivered in the absence of a pressure gradient. Substances that have been delivered to tissue using CED include proteins such as exotoxins, viruses, liposomes, oligonucleotides, and small molecule drugs such as known cytotoxic chemotherapeutic including paclitaxel, carboplatin, 1-(4-amo-2-me-thyl-5-pyrimidinyl)-methyl-3-(2-chlorethyl) 3-nitrosourea hydrochloride (i.e. ACNU, a nitrosourea), gemcitabine, and cytosine arabinoside.

[0014] Convection-enhanced delivery has also been used to deliver certain radioactively labeled proteins into cerebral tissues, including $^{131}$I-labeled toxins and antibodies. Such proteins bind to tissue macromolecules and thereby serve to fix the beta-particle-emitting $^{131}$I atom in such tissues. Once the radioactive protein is bound to the cancerous tissues, high energy ionizing radiation is emitted from the $^{131}$I atom, thereby penetrating a few millimeters in all directions from the position of such a tissue-bound radioisotope.

[0015] There have been many attempts to develop methods for delivery of $^{125}$IUDR, $^{125}$IUDR and related compounds to cancerous tissues. Direct introduction of $^{125}$IUDR to a tumor was first reported more than 30 years ago. See W D Bloomer and S J Adelstein, “Letter. Antineoplastic effect of iodine-125-labeled iododeoxyuridine,” Int J Radiat Biol Relat Stud Phys Chem Med, 27:509 (1975). Since that time, $^{125}$IUDR has been administered to animals with experimental tumors and human cancer patients via many routes of administration, and using a number of drug delivery methods. All of these studies notwithstanding, the obstacles associated with the delivery of $^{125}$IUDR and related compounds to solid tumors have yet to be overcome.

[0016] Attempts to make use of the systemic route of administration have been limited by the rapid metabolism and short lived pharmacokinetics of $^{125}$IUDR and related compounds. Attempts to make use of direct intra-tumoral injections have been limited by the rapid clearance of such compounds from tumor tissues, thereby providing only transient exposure to the cancer cells. Attempts to make use of sustained release biodegradable microspheres and low flow micro-infusion pumps have been limited by the fact that such methods depend entirely upon diffusion to distribute $^{125}$IUDR into the surrounding tissues from the depot or catheter tip. Diffusion provides $^{125}$IUDR distributions of only a few millimeters from the point of introduction, because such compounds are rapidly cleared from tissues.

SUMMARY

[0017] Various embodiments of the present invention provide methods for administration of Auger-electron emitting radioisotopically labeled nucleosides or analogs or produgs thereof (referred to herein as “Auger-electron emitting radio-nucleosides”) to cancerous target tissues, such as tissues of the brain, head or neck, pancreas, esophagus, intestines, bladder, ovary, or prostate gland, of a patient in need thereof. More specifically, in various embodiments methods are provided wherein a sustained, high-flow microinfusion delivery under pressure (“convection-enhanced delivery”) is used to deliver the Auger-electron emitting radionucleosides directly to cancerous target tissues via one or more catheters. Inventive methods of treating cancerous tissues use convection-enhanced delivery with a pressure sufficient to maintain flow rate of at least 0.5 $\mu$L/min, over a period of time, is used to deliver radioactive Auger-electron emitting nucleoside analogues directly into cancerous target tissues, such as the brain. In other cancerous tissues such as in head and neck tissues, pancreas, esophagus, intestines, bladder, ovary and prostate gland, it may be possible to treat with higher flow rates and a shorter duration of infusion than in the case of brain tissue. The microinfusion is delivered directly via the one or more catheters into the tissues containing cancer cells, and not into
a blood vessel that supplies the tissues. The Auger-electron emitting radionucleosides, as a constituent of the bulk liquid flow through the tissues induced by the pressure gradient, permeate the tissues more deeply and extensively than would take place by unpressurized diffusion. The radionucleosides are absorbed by cells undergoing DNA biosynthesis, wherein the very short-range Auger electrons bring about the irreparable destruction of DNA within those cells, directly bringing about the death of those cells. For the most part, adjacent cells and tissues are undamaged due to the very short effective range of this type of radiation. This method of administration avoids the very rapid clearance and metabolism of nucleosides and their analogs via the circulatory system. The method also avoids structural barriers that may exist within the body to transfer of a medicinal substance from the blood stream into the tissue, such as the blood-brain barrier, as is well known in the art. As mentioned above, it is well known that nucleosides and their analogs are both rapidly cleared from the blood stream, and in some cases can poorly penetrate tissues, for example brain tissues, from the blood stream due to barriers. As such, the inventive methods provide a uniquely advantageous method of using convection-enhanced delivery, as the Auger-emitting radionucleosides are extremely effective cytotoxic agents for cells undergoing DNA synthesis once they are taken up by a target cell, but are very poorly adapted for administration by conventional techniques, such as by oral administration, by injection into the blood stream, or by direct injection into cancerous tissues resulting only in a transient exposure to the target tissue after injection.

[0018] The bioactive agent, a solution of which is introduced into the target tissue through one or more catheters, consists of an Auger-electron emitter, such as $^{125}$I, wherein the radionucleide is incorporated into a nucleoside chemical entity that is adapted for uptake into the DNA of the target cells, in which case the short-range Auger electrons exert their destructive effects directly on the DNA within the cell in which they are contained, and with minimal collateral damage to surrounding cells. Examples include $^{122,124,125}$I-labeled iodouridineoxoriboside ($^{122,124,125}$IUDR, $^{122,124,125}$IUDR, and $^{122,124,125}$IUDR respectively). Another such radiochemical comprises an Auger electron emitter, such as a prodrg of $^{122,124,125}$IUDR, $^{122,124,125}$IUDR, or $^{122,124,125}$IUDR. Examples of prodrgs include various phosphate and carbonylate esters of the nucleosides.

[0019] Accordingly, various embodiments of the invention are directed to a method of treating cancer, comprising administering via high-flow pressurized microinfusion a bioactive agent comprising an Auger-electron emitting radionucleoside or an analog or prodrg thereof directly to a volume of tissue comprising cancerous cells within the body tissue of a patient, the method comprising: (a) disposing at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel; then, (b) delivering under a pressure to the tissue through each catheter a solution or suspension comprising the bioactive agent, wherein the pressure is sufficient to maintain a flow rate of the solution or suspension into the tissue of at least about 0.5 $\mu$L/min, for a period of time.

[0020] The inventive methods can be applied in the treatment of patients who have been screened and identified as having either a locally advanced stage solid tumor, a tumor wherein tumor processes have invaded surrounding non-cancerous tissue, or both. Accordingly, various embodiments of the invention provide a method of treating cancer, comprising administering, for treatment of cancer, a bioactive agent comprising an Auger-electron emitting radionucleoside or an analog or prodrg thereof directly to a volume comprising cancerous cells within the body tissue of a patient, the method comprising (a) selecting a patient afflicted with a locally advanced stage solid tumor or a cancer wherein tumor processes have invaded surrounding non-cancerous tissue; (b) disposing at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel; then, (c) delivering under a pressure to the tissue through each catheter a solution or suspension comprising the bioactive agent, wherein the pressure is sufficient to maintain a flow rate of the solution or suspension into the tissue of at least about 0.5 $\mu$L/min, for a period of time determined by the location of the cancerous tissue being treated.

[0021] In an embodiment of the invention a method of assembly of a system adapted for convection-enhanced delivery of an Auger-electron emitting radionucleoside or an analog thereof to a body tissue, comprising connecting a source of a pressurized liquid to a catheter adapted for intratissue delivery of a liquid under pressure, wherein the pressurized liquid comprises the Auger-electron emitting radionucleoside or analog thereof is provided.

DETAILED DESCRIPTION OF THE INVENTION

[0022] The “target tissue” refers to the diseased tissue into which the catheters are implanted. The “treatment field” is the 3-dimensional domain of tissue to be treated with the catheter or catheters. The treatment sub-field is the 3-dimensional domain of tissue supplied by a single catheter in the catheter array. The treatment field and target tissue can be the same.

[0023] “Cancer” or a “tumor”, as the terms are used herein, refer to a neoplasm or malignant growth of cells within a body tissue of a mammal, such as a human being. A “locally advanced stage solid tumor” is a malignant neoplasm that undergoes invasive growth, but has not yet extensively metastasized to distant sites in the body. A “tumor process” is a growth of cancerous cells extending into non-cancerous tissue from a malignant tumor, such as can result in invasion of surrounding tissue and expansion of the tumor.

[0024] The “fluid pharmaceutical agent” is a liquid containing $^{122,124,125}$IUDR, $^{122,124,125}$IUDR, or $^{122,124,125}$IUDR, a prodrg of $^{122,124,125}$IUDR, $^{122,124,125}$IUDR, or $^{122,124,125}$IUDR, or a related radioactive nucleoside analog, wherein the mode of radioactive decay includes emission of Auger electrons, (termed herein an “Auger-electron emitting radionucleoside”) adapted for incorporation into replicating DNA. The “fluid pharmaceutical agent” is infused from each catheter into the target tissues. Once the solution enters the tissues, it is referred to as the “infusate.”

[0025] “Auger electrons”, as are well known in the art, are relatively low energy (low energy with respect to most nuclear decay energies) electrons ejected from the electron shells surrounding the atomic nucleus, typically as a result of an electron capture process by an unstable atomic nucleus.

[0026] “Low flow micro-infusion” is defined as the direct infusion of a liquid into a tissue at a flow rate that is insufficient to generate bulk flow at the catheter tip. Low flow micro-infusion rates are generally below 0.5 $\mu$L/min.

[0027] “High flow micro-infusion” is defined as the direct infusion of a liquid into a tissue at a flow rate that is sufficient to create bulk flow at the catheter tip. High flow micro-infusion exceeds the rate at which the tissues can absorb the fluid pharmaceutical agent, and therefore such infusion pro-
duces “bulk flow” or “convection-enhanced delivery” of a fluid pharmacological agent within the interstitial compartment of the tissue. The extent of distribution of the fluid pharmacological agent within the tissue is substantially increased over that provided by diffusion alone. Thus, bulk flow or convection-enhanced delivery serves to supplement the distribution provided by diffusion to increase the overall distribution of the fluid pharmacological agent in the tissues. High flow micro-infusion rates are generally ≥0.5 μl/min. In cerebral tissues, high flow micro-infusion rates are generally between 0.5 and 15 μl/min. In certain non-cerebral tissues, which have increased tolerance to the potentially traumatic effects of high flow rate infusion, it may be desirable to use flow rates greater than 15 μl/min. With these higher flow rates it is possible to have individual treatments to the cancerous tissue be of durations shorter than one hour.

[0028] A “catheter” is a hollow or tubular structure, which can be implanted directly into the treatment field. A solution of a bioactive agent is introduced into the target tissue (treatment field) via the catheters. Catheters are hollow, having a lumen or central channel through which the solution flows from the liquid supply system into the tissue. A catheter comprises a tip, and one or more openings, apertures or ports at or relatively near the tip, or on any portion of the catheter adapted to be in direct contact with the tissue. A catheter may be linear or curvilinear, and is adapted for implantation into solid tissue of a patient. The catheter may comprise one or multiple thick segments, rings or bulges on the outside of the shaft to reduce backflow around the catheter track and thus promote uptake of the infusion into the tissue. The catheter may further comprise a non-cutting rounded tip to minimize trauma to tissues during implantation.

[0029] The base of the catheter can be connected via a “manifold” to the source of the pressurized liquid containing a pharmaceutical or radiochemical agent. The base of the catheter provides the route for delivery of liquid to the distal end of the catheter, which resides within the tissue after implantation.

[0030] The “catheter track” is a channel formed in the tissue as the catheter is advanced. The catheter track surrounds the catheter following implantation.

[0031] “Catheter arrays” are comprised of two or more catheters arranged in a specific configuration. Catheter arrays may have a pre-formed or fixed configuration that is established prior to implantation into the tissue. Alternatively, catheter arrays may be formed during the process of implantation when using a catheter guide system or catheter guide template. Catheter arrays can be parallel or radial (in positive or negative radial array, i.e., with the catheters radially directed inwards to a point within the tissue, or radially directed outwards from a point outside the tissue) arrangements of catheters, but may a variety of different patterns designed to treat the region around a tumor resection that is prone to tumor recurrence. The simplest catheter array has a brush-like configuration with at least two catheters.

[0032] The “catheter guide system” or “catheter guide template” with its catheter guide channels or catheter guide tubes accurately guides each catheter into its defined position within the tissue during implantation. Catheter guide templates can be used to implant one or a plurality of catheters into the target tissues. In instances wherein the catheter guide template is used to implant a plurality of catheters, such a device (a) provides pre-determined spacing between the catheters within a catheter array; (b) determines the relative orientation of the catheters with respect to each other as they enter the treatment field; and (c) determines the relative orientation (i.e. vector) of the catheters with respect to the target tissue.

[0033] The catheter guide template can be comprised of one or a plurality of catheter guide channels or catheter guide tubes into which the catheters are inserted for implantation. Catheter guide channels provide defined paths for the catheters to follow during implantation, and are adapted to allow relative motion of the catheters through the respective channels during catheter implantation. During implantation, the catheter tips emerge from the distal or efferent end of the catheter guide system. The operator controls implantation of the catheters at the proximal or afferent end of the catheter guide template. The effluent and afferent aspects of the catheter guide template may be designed with differently in each type of template system. In instances wherein the catheter guide template is used to implant a plurality of catheters, such a device provides at least two catheter guideways that determine the relative orientation of the catheters with respect to each other and with respect to the tissue into which the catheters are inserted. A guide template can provide for emplacement about 2, or about 4, or about 12, or about 24, or about 36 individual catheters.

[0034] Catheter guide channels are linear, curvilinear or dog-legged (i.e. bent) passages, tubes or holes that serve the purpose of directing individual catheters to a site of egress from the catheter guide system. In addition, these passages, channels give the catheter a vector upon egress from the catheter guide system.

[0035] Various embodiments of the invention are directed to a method of administering, for treatment of cancer, a fluid containing a bioactive agent comprising an Auger-electron emitting radionuclide, or an analog or a produg thereof, directly to a volume to tissue comprising cancerous cells within the body tissue of a patient, the method comprising: (a) disposing at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel; then, (b) delivering under pressure to the tissue through each catheter a solution or suspension comprising the bioactive agent, at a flow rate of at least about 0.5 μl/min, for a period of time determined by the location of the cancerous tissue being treated.

[0036] In various embodiments, the Auger-electron emitting radiolabeled nucleoside or an analog or a produg thereof (referred to hereinafter as an “Auger-electron emitting radionucleoside”), is 123I- or 125I-iododeoxy uridine (IUDR).

[0037] Delivery under pressure of the solution or suspension comprising the Auger-electron emitting radionucleoside can be accomplished using one or more catheters such that a spatial pressure gradient exists within the tissue and the solution permeates the tissue in response to the pressure gradient. The spatial pressure gradient drives the solution or suspension to penetrate the tissue, carrying with it the dissolved or dispersed Auger-electron emitting radionucleoside, into intimate contact with cells including cancerous cells disposed within the tissue. Cancerous cells, undergoing DNA biosynthesis and replication, can then take up the Auger-electron emitting radionucleoside and incorporate the compound into newly-synthesized DNA. Within the cancer cell, the Auger electrons, emitted by the decaying radionuclide, exert their destructive effect on surrounding biomolecules, resulting in decomposition of cellular DNA, which is necessary for cell survival. The short range of the Auger electrons ensures that
most of the destructive effect of the radioactive decay event is within that cell. Certain Auger-electron emitting radioisotopes such as \(^{125}\)I have half-lives in the order of hours (13.2 hr) such that within several days, most of the radioactive atoms have decayed. Other Auger-electron emitting radioisotopes such as \(^{153}\)I have half-lives in the order of days (59.4 d) such that decay events continue over the period of months or even years. Accordingly, the appropriate radioisotope can be selected for a particular use based on the half-life.

[0038] The catheter or catheters can be deployed within the patient's tissues, for example, within a void left by removal of a brain tumor, such that the catheters introduce into the tissue surrounding the tumor excision site. Alternatively, the catheter or catheters can be deployed into other tissues being infiltrated or invaded by individual cancer cells or groups of cancer cells, e.g., tissues in and around the esophagus, pancreas, intestines, bladder, head and neck region, a cancerous prostate gland, or into tumor plaques, such as occur in ovarian cancers. The entire system can be emplaced entirely within the patient's body, such that the liquid supply system and catheter are deployed under the patient's skin. Alternatively, the liquid pressurizer and/or liquid reservoir system may be deployed external to the patient's body. To the extent that the catheter or catheters come in contact with body tissue, it is preferred that at least the surface of catheter or catheters be biocompatible, as can be accomplished through the use of appropriate materials of construction. Likewise, to the extent that the liquid supply system is adapted to be disposed within the patient's body, its exterior surfaces can be biocompatible.

[0039] Various embodiments of the inventive method include the administration of the solution of the bioactive agent at a variety of pressures, flow rates, and durations of administration. For example, the solution can be administered continuously, intermittently, at various rates, and for various periods of time.

[0040] The combined features of the nanometer range Auger electrons, and the precise DNA-targeting mechanism of the nucleoside analogue, provide an extremely accurate and discriminating form of radiotherapy. Because of the short distance they travel, Auger electrons do not leave the nucleus after the incorporation of \(^{125}\)IUDR into DNA; there is essentially no crossfire within the tissues. If methods were available to deliver \(^{125}\)IUDR, \(^{123}\)IUDR and related compounds into cancerous tissues, this extremely accurate and discriminating type of radiation would be useful as a treatment for cancer. Based upon the extreme accuracy and discrimination DNA-bound Auger electrons, \(^{125}\)IUDR, \(^{123}\)IUDR, and related compounds are capable of eliminating individual cancer cells from the treatment field while sparing cells immediately adjacent to such target cells, and thereby preserving the tissues being invaded by the cancer cells.

[0041] The deposition of radiation on a nanometer scale, such as provided by locally administered liquid infusions of \(^{125}\)IUDR, \(^{123}\)IUDR and related compounds, cannot be achieved using conventional ionizing radiation, which penetrates millimeters to meters into tissues. Megavoltage x-ray beams or gamma photons penetrate completely through the body; proton beams penetrate into tissues for several centimeters; and high energy beta particles released by \(^{131}\)I- or \(^{90}\)Y-containing compounds penetrate tissues for about 2-5 millimeters in all directions from the point of deposition in cancerous tissue. Thus, x-ray beams, proton beams and beta particle-emitting isotopes, such as \(^{131}\)I- or \(^{90}\)Y, invariably expose normal cells inside and outside of the treatment field, and therefore such radiation treatment methods lack the microscopic accuracy needed to eliminate individual cancer cells from the treatment field.

[0042] The direct, definitive and broad spectrum mechanism by which \(^{125}\)IUDR, \(^{123}\)IUDR and related compounds kill cancer cells is well suited to eliminate cancer cells with a wide range of genetic and metabolic profiles and to eliminate cancer stem cells, which must replicate their DNA to maintain and drive the growth of the malignant tumor.

[0043] Auger-electron emitting radionucleides such as \(^{125}\)IUDR and \(^{123}\)IUDR are known to be rapidly metabolized, inactivated and cleared from the bloodstream. In addition, \(^{123}\)IUDR and related nucleoside analogues kill S-phase cells without any discrimination between replicating cancer cells and replicating normal cells. Such rapid metabolism and clearance from the bloodstream, and such a nonspecific cell killing mechanism, have precluded the use of such radioactive compounds as systemically administered anticancer agents; however, taken together with the short range Auger electrons emitted by such compounds, these properties are well suited for local delivery into cancerous tissues, such as using the inventive method comprising convection-enhanced delivery. Once such a radioactive compound is absorbed into the bloodstream, the risk of toxicity to replicating cells in normal tissues is minimized, due to the immediate dilution, metabolism and clearance of such a compound. The concentration of such a compound in the bloodstream is far below the concentration achieved in the cancerous tissues into which the radioactive agent was introduced. In addition, while some replicating normal cells may be present in the treatment field of certain cancerous tissues, the non-specific cell killing mechanism does not necessarily preclude the use of \(^{125}\)IUDR and related nucleoside analogues in the treatment of such tissues. Indeed, it is useful to kill some replicating, but non-malignant, cells in the treatment field, for example, the proliferating neovascular cells that nourish the malignant cells. Accordingly, the inventors herein have recognized that the Auger-electron emitted radionucleosides such as IUDR are unexpectedly exceptionally well-adapted for CED delivery to tumor-bearing tissues, for example to brain tissues. Among the wide variety of medicinal materials available for administration by CED, these IUDR-like compounds possess an unusual combination of properties that make them a hitherto-unrecognized exceptional selection for CED administration. This unique constellation of properties include a low diffusion rate through tissues in the absence of applied pressure, difficulty in penetration of internal barriers to diffusion such as the blood-brain barrier, rapid systemic dissemination and clearance of the radionucelides through the circulatory system, the rapid clearance of the radionucelides from tissues following local injections without the benefit of sustained bulk flow, and (among radiotherapeutic materials) a requirement that the radionucelides be taken into the cell and incorporated into DNA to exert a killing effect (unlike the situation with high-energy penetrating emissions from isotopes or from beams of photons or subatomic particles). In this way, delivery of Auger-electron emitting radionucelides such as \(^{122}\)IUDR and \(^{123}\)IUDR is achieved with unique and unexpected advantages through the use of the technique of convection-enhanced delivery. Such advantages would not be associated with, for example, CED high-flow microinfusion of \(^{131}\)Iodine-containing or \(^{90}\)Y-containing radioactive proteins or radioactive small molecules, including \(^{131}\)IUDR and other nucleoside analogs incorporating radionucelides.
topes that deliver more penetrating radiation, such as high energy beta particles, because such penetrating radiation would damage adjacent normal cells and tissues in addition to any destructive effect on target cells, due to the higher energy of beta particles as compared to Auger electrons.

In addition, the use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within the treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons, proton beams or beta electrons that penetrate the tissues in and around the treatment field. Currently available radiotherapy methods involve types of radiation that penetrate tissues for distances far greater than Auger electrons. Gamma photons pass completely through the body; proton beams usually penetrate several centimeters into tissues; and beta electrons usually penetrate 3-5 millimeters into tissues. Furthermore, currently available radiotherapy methods result in the ionization of water molecules throughout the path of the radiation as it penetrates normal tissues en route to the intended treatment field. Ionization of water produces free radicals, such as hydroxyl ions and superoxide ions, throughout the path of the radiation. The free radicals mediate the therapeutic and toxic effects of such radiation by damaging DNA and other macromolecules in the cells throughout the path of radiation. For these reasons, ionizing radiation lacks the microscopic accuracy needed to eliminate individual cancer cells from the treatment field. Such collateral damage stands in the way of organ preservation.

Auger electrons, the active principle of present invention, do not penetrate tissues in the form of a radiation beam. This unusual type of radiation is delivered into the tissues in a liquid vehicle, and thereby carries such short range radiation to the target cells. The present invention does not depend upon water ionization or the generation of free radical intermediates, which indirectly damage the DNA of the target cells. The present invention uses short range Auger electrons that directly and irreparably destroy the DNA of the target cells. The present inventive method combines an infusible liquid vehicle and extremely short range electrons capable of destroying any replicating target cells in the treatment field. The present invention comprises a new form of radiotherapy for the treatment of solid tumors. Unlike currently available forms of radiotherapy, this new form of radiotherapy has the submicronscopic accuracy needed to eliminate individual cancer cells from the treatment field, and thereby preserve the structure and function of the cancerous tissues being treated.

The delivery under pressure of the solution or suspension containing the Auger-electron emitting radionuclide is carried out at pressures, and for periods of time, sufficient to cause bulk flow of the solution or suspension through surrounding tissues. The relationship of pressure to flow rate will depend, at least in part, upon factors such as the density and porosity of the target tissue, the position of implantation within the tissue of the one or more catheters, and the viscosity of the solution or suspension being delivered to the tissues. Flow rates of at least about 0.5 μL/min, over a period of time of at least about 1 hour within brain tissue, can result in the formation of a pressure gradient within the tissue that drives the bulk flow of the solution through the tissue. Flow rates can be higher, for example up to about 15 μL/min, to provide the necessary pressure gradient within brain tissue. The flow rate may be greater than 15 μL/min in cancerous tissues in other sites within the body. The sustained period under which the pressurized liquid is applied directly within the tissue is at least about one hour in the brain, sufficient to establish the pressure gradient. Cancerous tissues outside the brain may allow the use of higher flow rates and pressure gradients that will result in shorter durations of infusion sufficient to produce convective flow throughout the treatment field. The pressure can be applied constantly or intermittently over the period of time. The period of time can be significantly longer than an hour, such as days or weeks, ranging up to about six months or even a year. The pressure can be applied to the liquid for a shorter period of time, released, and then reapplied.

The relationship of pressure applied versus time yields a temporal pressure profile. This profile can be constant, i.e., a particular pressure is applied and maintained without change over time. Alternatively, the pressure profile can be linear with a positive slope, i.e., the pressure is steadily increased over a time period, or can also include linear negative slopes, as the pressure is constantly decreased over a time period. Or, the pressure can be applied to produce sinusoidal flow profiles in the tissues. Or, the pressure can be increased or decreased stepwise over time, or exponentially over time, or any other temporal pressure profile that provides suitable permeation of the tissue by the solution or suspension under pressure. The pressure profile can be created through the use of a digitally controlled pump, such that the profile selected can be implemented through a computer-controlled interface. The particular profile that may be most well adapted for treating a type of cancer, or a tissue location, or both, can be determined based on observations of the distribution of the Auger-electron emitting radionuclide in the patient under treatment and in previous patients with similar conditions who were treated using the inventive methods. Isotopes such as 125I and 121I emit, in addition to Auger electrons, photons of X-ray/gamma ray frequencies that can be used in spatial imaging techniques such as single photon emission computed tomography (SPECT). As a result, a database of permeation rates and depths for treatments applied in various tissue types and locations and under various clinical circumstances can be accumulated over time, allowing the practitioner to select a pressure profile and duration of administration, as well as a concentration of the Auger-electron emitting radionuclides and a medium for their delivery, based on this information. However, any degree of permeation beyond that very minimal amount that can be achieved by passive, unpressurized diffusion, or by systemic administration via the circulatory system, will provide for an enhanced effectiveness due to the delivery of the cancer cell-killing material to a greater number of cancer cells within the larger volume of affected body tissue, such as brain or prostate tissue. Furthermore, unlike direct injections using syringe needles, convective-enhanced delivery provides a method by which to introduce such compounds into tumors over a sufficient period of time to expose cancer cells as they enter S-phase of the cell cycle; this may take several weeks or several months depending upon the cell cycle kinetics of the particular tumor being treated.

The ability of the inventive methods to deliver such compounds into cancerous tissues and directly to rapidly dividing tumor cells within a significant volume of otherwise inaccessible body tissue can reduce or even eradicate locally advanced solid tumors through the selective killing of substantially all dividing cells by a mechanism for which resis-
tance is extremely unlikely to develop. And, due to the very short-range nature of the killing effect of Auger electrons, collateral damage to healthy tissues, particularly in situations where little normal cell division is taking place, such as brain tissue, larger doses of such radiation can be administered with reduced side-effects. Once the targeted cells die and decompose, any residual undecayed radionucleoside material is rapidly and effectively cleared from the tissue by normal body processes.

Accordingly, various embodiments of the invention provide a method of treating cancer, comprising: administering, for treatment of cancer, a bioactive agent comprising an Auger-electron emitting radionucleoside or an analog or prod- drug thereof directly to a volume to tissue comprising can-
cerous cells within the body tissue of a patient, the method comprising: (a) selecting a patient afflicted with an advanced stage solid tumor or a cancer wherein tumor processes have invaded surrounding non-cancerous tissue; (b) disposing at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel; then, (c) delivering under a pressure to the tissue through each catheter a solution or suspension comprising the bioactive agent, wherein the pressure is sufficient to maintain a flow rate of the solution or suspension into the tissue of at least about 0.5 μl/min, for a period of time dependent on the location of the cancerous lesion.

The inventive methods are particularly advantageous in the treatment of patients afflicted with tumors wherein tumor processes have invaded adjacent non-cancerous tissues. Using an embodiment of the invention, a volume of tissue, for example brain tissue in a patient afflicted with glioblastoma multiforme, can be suffused with the Auger-electron emitting radionucleoside. The tissue contains both non-cancerous cells, which are typically not dividing or are dividing at a very low rate, and tumor processes including rapidly dividing cancerous cells. The high-flow microinfusion of the radionucleoside serves to surround all these cells with the radionucleoside, but only those cells undergoing cell division take up and retain the radionucleoside effectively. Accordingly, it is the cancerous cells that are predominantly destroyed, as uptake and incorporation of the radionucleoside into cellular DNA is necessary for cell death. In this way, micro-regions of cancerous cells disposed within normal tissue can be selectively treated with less collateral damage than if molecular sources of more penetrating radiation, such as beta-emitting isotopes, or beams of energetic particles (protons, muons, etc.) or photons (X-ray, gamma ray) were used.

The Auger-electron emitting radionucleosides can be delivered using CED techniques including the use of a single catheter, or use of a plurality of catheters each being responsible for delivery to a zone of tissue. In cases in which multiple catheters are used, a more uniform treatment field is possible, since each individual catheter delivers the therapeutic agent to one part of the treatment field, also referred to as the sub-treatment field. Overlapping sub-treatment fields provide a complete and more uniform treatment field. See U.S. "Catheter and Array for Anticaner Therapy", U.S. Patent Ser. No. 60/895,916, filed Mar. 20, 2007, by the inventors herein, incorporated herein by reference in its entirety. However, even a single catheter can deliver a solution under pressure, and can be used to achieve the unexpected advantage accruing by the selection of the Auger-electron emitting radionucleosides, as recognized by the inventors herein.

Numerous Auger electron emitting deoxyribo-
nucleosides may be used, including but not limited to: 5-[125]iodouridine 2'-deoxyribonucleoside (IUDR), 5-[123]iodouridine 2'-deoxyribonucleoside (IUDR), 5-[125]iodouridine 2'-deoxyribonucleoside (IUDR), 5-[125]Br-bromouridine 2'-deoxyribonucleoside (BUDR), 5-[32P]Br-bromouridine 2'-deoxyribonucleoside (BUDR), 8-[125]iododeoxyadenosine 2'-deoxyribonucleoside and 5-[125]Br-
bromodeoxadenosine 2'-deoxyribonucleoside. In addition, alpha particle emitting deoxyribonucleosides that emit Auger electrons may be used, including but not limited to 5-[32P]AT-
astatouridine 2'-deoxyribonucleoside (211AtUDP).

In addition, a produg of an Auger-electron emitting nucleoside can also be delivered using the inventive method disclosed herein. This includes a wide selection of phosphate and carbonyl esters involving the 5' and 3' hydroxyl groups on the ribose moiety of the nucleosides. For example, see “Cancer specific radiolabeled conjugates regulated by the cell cycle for the treatment and diagnosis of cancer” (US patent 20050069495) and "Formulations for cell cycle dependent anticancer agents" (U.S. patent application Ser. No. 11/222,668/PCT/US04/07650). Such produgs are hydrolyzed by nucleases, and in many cases by ubiquitous esterases, thereby releasing the active forms of such nucleo-
sides, which after uptake by cells, are re-phosphorylated, recognized by cellular DNA polymerases and then incor-
porated into newly synthesized DNA. It is understood that a variety of chemical modifications of the nucleoside ana-
logues containing the Auger or alpha particle emitting nuclides described above may be delivered using the devices disclosed herein. For example, nucleosides containing a 3' deoxyribose may be incorporated at the terminal position of a growing strand of DNA prior to chain termination. Finally, it is understood that the ribose or base moieties of deoxynucleo-
side analogues such as 125IUDR or 123IUDR may be modified in numerous ways without necessarily interfering with their incorporation into newly synthesized DNA.

The fluid pharmacological agent is introduced into the portal tubing system using a mechanical pump, osmotic pump, syringe, or any device capable of generating hydro-
static pressure. Preferably, the pump and reservoir are inside the body, but may also be outside the body.

The catheter or plurality of catheters is adapted to remain within the tissue for a period of time. By this is meant that a catheter does not function merely analogously to a syringe needle, which is inserted into tissue, a material injected, and the needle immediately withdrawn. Rather, the catheter or catheter array within the target tissue is left in place for a period of hours, or of days, weeks, or even months, during which a solution of a bioactive agent, such as 125IUDR, 123IUDR or a related compound, is introduced into the tissue under a certain amount of pressure, that is sufficient to enhance permeation of the tissue by the solution. Typically, resistance to liquid flow into tissue is relatively high, so absolute delivery rates are relatively low compared to a typical injection with a hypodermic syringe needle. On the other hand, the rate of liquid flow into the tissue needs to be suffi-

The fluid pharmacological agent is infused from each catheter into cerebral tissues at a rate between 0.5 and 15 μl/min. The fluid pharmacological agent may be infused into non-cerebral tissues at rates of at least 0.5 μl/min, due to a
higher potential tolerance of such tissues to the mechanical stresses associated with the use of high flow micro-infusion methods. Each of the catheters remains within the tissue for a period of time sufficient to treat a target tissue volume with a desirable level of the particular bioactive agent being used in the particular situation.

Alternatively, the fluid pharmacological agent may be discharged continuously from the catheters into the tissues as a result of a continuous pressure gradient generated and maintained by the infusion pump. In the latter case, the pressure gradient is maintained throughout the delivery of the agent, thereby producing continuous bulk flow of the fluid pharmacological agent into the tissue. The fluid pressure may be increased in one or more steps, increased continuously over at least part of the infusion period, or increased over all of the entire infusion period.

The fluid pharmacological agent may be infused for duration of at least 15 minutes; for 1 hour; for 2 hours; for 4 hours; for 6 hours; for 8 hours; for 10 hours; for 12 hours; or for 24 hours. Alternatively, the fluid pharmacological agent may be infused continuously for 2 days; for 7 days; for 14 days; for 28 days; for 56 days; for 180 days; or for 365 days. In addition, the fluid pharmacological agent may be infused for a duration of less than one hour if the treatment is located outside the brain.

The fluid pharmacological agent may be discharged repetitively or intermittently from the catheter or catheters into the tissues as a result of fluid pressure generated by the infusion pump. The increased fluid pressure may be instantaneous or brief in duration, thereby producing a rapid infusion of the fluid pharmacological agent into the tissue. Alternatively, the pressure gradient may be more sustained, but not maintained continuously throughout the delivery of the agent, thereby producing one or more fluid waves that carry the fluid pharmacological agent into the tissue. In either case, the intervals between the repetitive or intermittent discharges of fluid may be brief (e.g. one second) or longer (e.g. several hours or several days). The latter are examples of pulsed delivery of the fluid pharmacological agent into tissue.

The fluid pharmacological agent may be infused using various repetitive intermittent schedules of administration. For example, the fluid pharmacological agent may be infused for 2 hours followed by an interval of 2 hours during which the infusion is stopped; or for 2 hours followed by an interval of 4 hours without infusion; or for 2 hours followed by an interval of 6 hours without infusion; or for 2 hours followed by an interval of 8 hours without infusion; or for 2 hours followed by an interval of 10 hours without infusion; or for 4 hours followed by an interval of 12 hours without infusion.

Alternatively, the fluid pharmacological agent may be infused for 4 hours followed by an interval of 4 hours during which the infusion is stopped; or for 4 hours followed by an interval of 6 hours without infusion; or for 4 hours followed by an interval of 8 hours without infusion; or for 4 hours followed by an interval of 10 hours without infusion; or for 4 hours followed by an interval of 12 hours without infusion.

Alternatively, the fluid pharmacological agent may be infused for 8 hours followed by an interval of 6 hours during which the infusion is stopped; or for 8 hours followed by an interval of 8 hours without infusion; or for 8 hours followed by an interval of 10 hours without infusion; or for 8 hours followed by an interval of 12 hours without infusion.

Alternatively, the fluid pharmacological agent may be infused for 10 hours followed by an interval of 6 hours during which the infusion is stopped; or for 10 hours followed by an interval of 8 hours without infusion; or for 10 hours followed by an interval of 10 hours without infusion; or for 10 hours followed by an interval of 12 hours without infusion.

Alternatively, the fluid pharmacological agent may be infused for 12 hours followed by an interval of 6 hours during which the infusion is stopped; or for 12 hours followed by an interval of 8 hours without infusion; or for 12 hours followed by an interval of 10 hours without infusion; or for 12 hours followed by an interval of 12 hours without infusion.

According to another embodiment of the invention, the fluid pharmacological agent may be discharged as a brief injection, a pulse, or as a more sustained infusion into the tissues, and then followed by an infusion of fluid that does not contain the fluid pharmacological agent. The fluid lacking a pharmacological agent may be introduced into the tissue by one or more instantaneous injections, one or more sustained waves of fluid movements, or by continuous bulk flow that is maintained by a constant pressure gradient.

The fluid pharmacological agent may comprise 123IUDR, 132IUDR or a related radioactive nucleoside analogues at a concentration between 1 picomole/liter (1 pM) and 1 millimole/liter (1 mM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 500 micromolar/liter (500 μM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 50 micromolar/liter (50 μM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 10 micromolar/liter (10 μM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 1 micromolar/liter (1 μM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 500 nanomolar/liter (500 nM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 50 nanomolar/liter (50 nM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 10 nanomolar/liter (10 nM); or the fluid may contain such compounds at concentrations between 1 picomole/liter (1 pM) and 1 nanomolar/liter (1 nM); or the fluid may contain such compounds at concentrations between 1 and 500 picomole/liter (1 pM-500 pM); or the fluid may contain such compounds at concentrations between 1 and 50 picomole/liter (1 pM-50 pM); or the fluid may contain such compounds at concentrations between 1 and 10 picomole/liter (1 pM-10 pM).

The solution or suspension containing the Auger-electron emitting radionucleoside can contain further constituents, such as liposomes, surfactants, salts, and the like. The solution or suspension can also include additional medicinal substances for delivery to the afflicted tissue, such as anti-inflammatory agents, antibiotics, and the like.

All publications, patents, and patent documents cited in the specification are incorporated by reference herein, as though individually incorporated by reference. In the case of any inconsistencies, the present disclosure, including any definitions therein, will prevail. The invention has been
described with reference to various non-limiting examples and embodiments. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the present invention.

EXAMPLES

[0070] The present invention will be described with reference to the following non-limiting examples.

Example 1

Treatment of Malignant Brain Tumors Above the Tentorium Cerebelli

[0071] High grade malignant gliomas, including the most common malignant glioma subtype, referred to as “glioblastoma multiforme”, are locally advanced solid tumors originating in the brain. In adults, glioblastoma multiforme tumors usually arise in the cerebral tissues situated above the tentorium cerebelli, a tent-like sheet of fibrous tissue that separates the cerebrum from the underlying cerebellum and brainstem. Glioblastoma multiforme tumors are among the most aggressive, treatment-resistant and devastating types of tumors known. The inexorable infiltration of tumor cells into otherwise functional cerebral tissues surrounding the primary tumor causes progressive impairment of neurological functions, and nearly always leads to death within a year or less.

[0072] Such tumors rarely, if ever, metastasize to sites outside of the cranium. Glioblastoma multiforme tumors usually recur close to the site of the original tumor. In fact, after surgical removal of most of the tumor tissue, and following adjuvant radiation therapy with or without the addition of drugs such as temozolomide or carboplatin, approximately 90% of glioblastoma multiforme tumors recur within 2 centimeters of the surgical margin of the tumor resection cavity. More extensive surgery to remove all of the cancer cells might prolong survival, but at the cost of removing too much functional brain tissue. In this situation, organ preservation is crucial.

[0073] Glioblastoma multiforme is a frustrating problem, because the tumor essentially always recurs, and the most likely site of the recurrence is known in advance. There are currently no methods to prevent tumor recurrence, or to eliminate the tumor cells after a recurrence has occurred. Indeed, the vast majority of patients with such tumors die as a result of local tumor recurrences.

[0074] The 2 centimeter rim of tissue surrounding the tumor resection cavity may be referred to as the “treatment field”, because such tissue constitutes the most likely site of tumor recurrence. The present invention provides methods by which to deliver Auger electron-mediated radiotherapy, for example 125I-UDR, to the treatment field using a liquid vehicle that penetrates such tissues by the force of bulk flow. The use of a liquid vehicle to locally deliver Auger electron-mediated radiotherapy to the treatment field distinguishes this form of radiotherapy from currently available forms of local radiotherapy.

[0075] The liquid vehicle delivers 125I-UDR to normal and malignant cells within the treatment field. Once in the treatment field, the 25I-UDR kills those cells that are engaged in DNA synthesis and spares the cells that are not engaged in DNA synthesis. Within the brain tumor treatment field, DNA synthesis occurs essentially only in the malignant cells and the blood vascular cells that are associated with the malignant cells. The present invention makes use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating target cells within the treatment field.

[0076] The method by which the 125I-UDR-containing liquid vehicle is delivered into the treatment field involves the use of one or more catheters. After the main tumor is removed surgically, in a procedure referred to as “debulking surgery”, one or more catheters are inserted into the wall of the tumor resection cavity, i.e. into the treatment field. A range of catheter sizes may be used; in general, 23-31 gauge catheters are well suited for this method. The catheters are usually advanced 0.5 to 3.0 cm into the cerebral tissues. Digital pretreatment planning, including the use of intra-operative navigation with a radiofrequency probe, may be used to optimize the position and depth of the catheters. The catheters are preferably spaced closely enough together that the distance between them is no greater than about twice the distance over which the bioactive agent can therapeutically penetrate the tissue. The proximal ends of the catheters converge upon a manifold that is connected to a tube, which leads to a digitally programmable pump system equipped with a reservoir. The entire system may be surgically implanted beneath the skin.

[0077] The pump and reservoir system, usually located under the skin of the trunk or abdomen, may be filled weekly or biweekly with a solution of 125I-UDR that is introduced trans-cutaneously via a port leading into the reservoir. A range of 125I-UDR concentrations may be used; in general, the concentration of 125I-UDR is between 100 pM and 500 nM.

The pump is programmed to infuse the 125I-UDR solution at a flow rate of 0.5-15 μl/min per catheter as needed to generate bulk flow within the target tissue. A variety of treatment schedules may be used including continuous infusion, or a variety of intermittent schedules. A preferred schedule of administration is 6 hours of infusion (ON) followed by 6 hours without infusion (OFF).

[0078] The use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within a brain tumor treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons or proton beams that usually must pass through the normal tissues in and around the treatment field. The use of a liquid vehicle to deliver Auger-electron emitting nucleoside analogues is a new form of radiotherapy for the treatment of malignant tumors above the tentorium cerebelli.

Example 2

Treatment of Malignant Brain Tumors Below the Tentorium Cerebelli

[0079] In young children, gliomas and other malignant tumors often arise in the cerebellum and brainstem, which are situated below the tentorium cerebelli, a tent-like sheet of fibrous tissue that separates the cerebrum from the underlying cerebellum. Such “subtentorial brain tumors” are difficult to treat. First, subtentorial tumors are located deep in the brain, which makes such tumors relatively inaccessible to the surgeon. Second, subtentorial tumors often invade the delicate neural tracts that converge upon this particular region of the central nervous system. For these reasons, subtentorial tumors are inoperable. In addition, the delicate neural tracts in this region of the brain are highly sensitive to the toxic effects of ionizing radiation. Many systemic drugs cannot penetrate the blood-brain-barrier; and even when this occurs, such drugs may have minimal activity against subtentorial brain tumors. Therefore, treatment options for such patients are
limited. The infiltration of tumor cells into otherwise functional neural tissues in this part of the brain causes progressive impairment of neurological functions, and nearly always leads to death within a year or less.

The present invention provides methods by which to deliver Auger electron-mediated radiotherapy, for example using $^{125}$IUDR, to malignant tumors that have infiltrated into the delicate neural tissues located below the tentorium cerebelli. The present invention provides methods by which to deliver Auger electron-mediated radiotherapy into subtentorial treatment fields using a liquid vehicle that penetrates such tissues by the force of bulk flow.

The liquid vehicle delivers $^{125}$IUDR to normal and malignant cells within the subtentorial treatment field. Once in the treatment field, the $^{32}$PUDR kills those cells that are engaged in DNA synthesis and spares the cells that are not engaged in DNA synthesis. Within the subtentorial treatment field, DNA synthesis occurs principally in the malignant cells and the blood vascular cells that are associated with the malignant cells. The present invention makes use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating target cells within the treatment field.

One or more catheters are introduced from a point of entry on the surface of the corpus callosum located between the cerebral hemispheres. The catheter(s) may be advanced towards the brainstem under stereo-tactic guidance using intra-operative navigation with a radiofrequency probe. The catheter tip(s) first penetrate the basal ganglia, and then enter the rostral portion of the pons. The position of the catheter tip(s) may be optimized using in intra-operative navigation. A range of catheter sizes may be used; in general, 14-31 gauge catheters are well suited for this method. The catheter(s) may be advanced into the pons or deeper into the brainstem. Alternatively, the catheter(s) may be advanced in a posterior direction into the cerebellum. The catheter(s) are preferably spaced closely enough together that the distance between them is no greater than about twice the distance over which the bioactive agent can therapeutically penetrate the tissue. The proximal catheter(s) converge upon a manifold that is connected to a tube, which leads to a digitally programmable pump system equipped with a reservoir. The entire system may be surgically implanted beneath the skin.

The pump and reservoir system, usually located under the skin of the trunk or abdomen, may be filled weekly or biweekly with a solution of $^{125}$IUDR that is introduced trans-cutaneously via a port lead into the reservoir. A range of $^{125}$IUDR concentrations may be used; in general, the concentration of $^{125}$IUDR is between 100 pM and 500 nM. The pump is usually programmed to infuse the $^{125}$IUDR solution at a flow rate of 0.5-15 µl/min per catheter as needed to generate bulk flow in the target tissues. A variety of treatment schedules may be used including continuous infusion or one of a variety of intermittent schedules. A preferred schedule of administration is 6 hours of infusion (ON) followed by 6 hours without infusion (OFF).

The use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within a subtentorial treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons or proton beams that usually must pass through normal tissues in and around the treatment field. The use of a liquid vehicle to deliver Auger-electron emitting nucleoside analogues is a new form of radiotherapy for the treatment of malignant tumors below the tentorium cerebelli.

Example 3

Treatment of Locally Advanced Pancreatic Cancer

Most pancreatic tumors arise in the head of the pancreas (70%), but may also arise in the body (20%) or tail (10%) of the pancreas. The majority of pancreatic tumors are locally advanced at the time of diagnosis. Such tumors have invaded into one or more of the peri-pancreatic tissues, such as the lymph nodes, blood vessels and nerves associated with the celiac axis; the superior mesenteric artery and superior mesenteric vein; the portal vein; the splanchic nerves; the duodenum; the stomach; bile duct system; and retroperitoneum. Pancreatic tumors tend to remain localized to the peri-pancreatic tissues, but some tumors metastasize to the liver, sites in the peritoneum, and occasionally to the lungs.

Some pancreatic tumors can be removed surgically, such as tumors that cause early symptoms such as blockage of the bile ducts. Such tumors are usually restricted to the head of the pancreas and/or have invaded only the duodenum, thereby permitting complete removal of the tumor cells. Potentially curative surgery is possible in only about 10% of patients. Most pancreatic cancers are not surgically resectable, and treatment is aimed at alleviating symptoms. Currently available treatments include chemotherapy with gemcitabine, or 5-fluorouracil combined with external beam radiotherapy. Tumor infiltration of the splanchic nerves leads to progressive severe pain, which is treated with pain medications. Chemotherapy and radiotherapy may also mitigate pain to some extent. Despite the fact that pancreatic cancer tends to remain localized, such tumors are deadly with most patients surviving only about 6 months after the diagnosis. Most patients die of hemorrhage due to invasion of the tumor into blood vessels or infection associated with the treatments used to treat the cancer.

The present invention provides methods by which to deliver Auger electron-mediated radiotherapy, for example using $^{125}$IUDR, to locally-advanced pancreatic cancers that have infiltrated into the peri-pancreatic tissues, but which have not yet metastasized to distant tissues. The present invention provides methods by which to deliver Auger electron-mediated radiotherapy into the peri-pancreatic treatment field using a liquid vehicle that penetrates such cancerous tissues by the force of bulk flow.

The present invention is preferably used in patients who have had partial or complete surgical resection of the pancreas, but removal of the pancreas may not be indicated in all patients. The liquid vehicle delivers $^{125}$IUDR to normal and malignant cells within the peri-pancreatic treatment field. Once in the treatment field, the $^{32}$PUDR kills those cells that are engaged in DNA synthesis and it spares the cells that are not engaged in DNA synthesis. Within the peri-pancreatic treatment field, DNA synthesis occurs principally in the malignant cells and the blood vascular cells that are associated with the malignant cells. The present invention makes use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating target cells within the peri-pancreatic treatment field.

The treatment field is essentially the same region that would usually be treated with external beam radiation. The 3-dimensional treatment field is mapped using preoperative CT and/or MRI. The procedure for implanting the cath-
eters into the treatment field may involve a laparotomy to gain access to the cancerous tissues, which are often deep in the abdominal cavity with possible extensions into the retroperitoneum. In other cases, catheters may be implanted into such cancerous tissues using video-assisted endoscopic techniques. Cancerous tissues tend to have a white or light tan color and a more firm texture than the uninvolved tissues within the peri-pancreatic region. Usually multiple catheters are introduced into the treatment field. A range of catheter sizes may be used; in general, 14-31 gauge catheters are well suited for this method. The catheter(s) are preferably spaced closely enough together that the distance between them is no greater than about twice the distance over which the bioactive agent can therapeutically penetrate the tissue. The proximal catheter(s) converge upon a manifold that is connected to a tube, which leads to a digitally programmable pump system equipped with a reservoir. The entire system may be surgically implanted beneath the skin.

The pump and reservoir system, usually located under the skin of the abdomen, may be filled weekly or biweekly with a solution of 125IUDR that is introduced transcutaneously via a portal leading into the reservoir. A range of 125IUDR concentrations may be used; in general, the concentration of 125IUDR is between 100 μM and 500 μM. The pump is usually programmed to infuse the 125IUDR solution at a flow rate greater than 0.5 μl/min per catheter, as needed, to generate bulk flow in the target tissues. A variety of treatment schedules may be used including continuous infusion or one of a variety of intermittent schedules. A preferred schedule of administration is 6 hours of infusion (ON) followed by 6 hours without infusion (OFF).

The use of an infusable liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within a peri-pancreatic treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons or proton beams that usually must pass through normal tissues in and around the treatment field. The use of a liquid vehicle to deliver Auger-electron emitting nucleoside analogues is a new form of radiotherapy for the treatment of pancreatic cancer.

Example 4

Treatment of Early Stage and Locally Advanced Prostate Cancer

The majority of prostate cancers are diagnosed at an early stage with the cancer still confined to the prostate gland. Increasingly early detection is due to the widespread use of prostate specific antigen screening in men over the age of 50. After receiving definitive treatments such as external beam radiation, brachytherapy, or prostatectomy for localized disease, the cancer may recur and progress as indicated by a rising level of prostate specific antigen in the blood. In such patients, the tumor may have spread beyond the capsule of the prostate gland, and may have infiltrated peri-prostatic pelvic tissues including the base of the bladder; the vas deferens; the ejaculatory ducts; the seminal vesicles; the pelvic tissues adjacent to the bladder or bowel; and/or into the pelvic lymph nodes. In the next stage, the prostatic cancer cells spread to distant metastatic sites, such as the bones and distant lymph nodes. The present invention provides methods by which to deliver Auger electron-mediated radiotherapy, for example using 125IUDR, to early stage or locally-advanced prostate cancers that have not yet metastasized to distant tissues.

In the case of early stage disease, for example in an elderly man with a desire to avoid the potentially serious side effects of radiotherapy or prostatectomy (e.g. impotence and rectal incontinence), the present invention provides methods by which to deliver Auger electron-mediated radiotherapy into the prostate gland using a liquid vehicle that penetrates such tissues by the force of bulk flow. The liquid vehicle delivers 125IUDR to normal and malignant cells within the prostate gland. Once in the prostate gland, the 125IUDR kills those cells that are engaged in DNA synthesis and it spares the cells that are not engaged in DNA synthesis. Within the prostate gland, DNA synthesis takes place in the cancer cells and in the normal glandular epithelium, but most of the normal cells are expendable and not necessary for a healthy existence. Therefore, the liquid vehicle containing 125IUDR may be provided to both the normal and malignant cells within the prostate gland.

In patients with early stage prostate cancer, the catheters are inserted beneath the capsule of the prostate gland such that the convective treatment fluid permeates the interstitial tissues of the gland, while minimizing the escape of fluid into the duct system. Most prostate cancers arise in the posterior lobes of the prostate gland, and the posterior lobes are generally more accessible than the anterior aspect of the gland. The posterior lobes of the prostate gland are immediately anterior to the rectum, and below the recto-vesical fascia, which forms a pocket-like gap between the posterior aspect of the bladder and the rectum. Although the prostate gland is not immediately accessible from within the pelvic peritoneal cavity, the posterior lobes can be accessed via the recto-vesical fascia. Alternatively, the posterior lobes of the prostate gland can be accessed from the perineal approach.

According to one method, the catheters may be implanted beneath the prostate capsule from the supra-pubic approach using either conventional surgical techniques or minimally invasive techniques such as video-assisted endoscopic manipulations. The catheters may be implanted by first penetrating the recto-vesical fascia, from above, on the posterior aspect of the bladder. Alternatively, the catheters may be implanted under the prostate capsule from other approaches, such as via the perineum. Other approaches, such as via transurethral or transrectal incisions, are also possible.

In some patients with locally advanced prostate cancer, the prostate gland may have been removed surgically. In other instances, the prostate gland may have been left in place. In either case, the 3-dimensional treatment field is mapped using preoperative CT and/or MRI. Thereafter, the catheters are inserted into the cancerous tissues within the pelvis using the supra-pubic, perineal or other surgical approaches. As in the case of early stage prostate cancer, catheter insertion may be accomplished using conventional surgical techniques or minimally invasive techniques such as video-assisted endoscopic manipulations.

Usually multiple catheters are introduced into the treatment field. A range of catheter sizes may be used; in general, 14-31 gauge catheters are well suited for this method. The catheter(s) are preferably spaced closely enough together that the distance between them is no greater than about twice the distance over which the bioactive agent can therapeutically penetrate the tissue. The proximal catheter(s) converge upon a manifold that is connected to a tube, which leads to a digitally programmable pump system equipped with a reservoir. The entire system may be surgically implanted beneath the skin.
The pump and reservoir system, usually located under the skin of the abdomen, may be filled weekly or biweekly with a solution of $^{125}$IUDR that is introduced transcutaneously via a portal leading into the reservoir. A range of $^{125}$IUDR concentrations may be used; in general, the concentration of $^{125}$IUDR is between 100 pM and 500 nM. The pump is usually programmed to infuse the $^{125}$IUDR solution at a flow rate greater than 0.5 μl/min per catheter, as needed to generate bulk flow in the target tissues. A variety of treatment schedules may be used including continuous infusion or a variety of intermittent schedules. A preferred schedule of administration is 6 hours of infusion (ON) followed by 6 hours without infusion (OFF).

The use of an infusible liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within a prostate gland or peri-prostatic treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons or proton beams that usually must pass through normal tissues in and around the treatment field. The use of a liquid vehicle to deliver Auger-electron emitting nucleoside analogues is a new form of radiotherapy for the treatment of prostate cancer.

Example 5

Treatment of Locally Advanced Head and Neck Cancer

Malignant tumors may arise in numerous mucosal sites in the head and neck region, for example, in the oral cavity, the tongue, the oropharynx, nasopharynx, hypopharynx, larynx, etc. Early stage head and neck cancers can usually be cured by surgery or external beam radiation, but if patients can be cured once the tumor has invaded extensively into local tissues. Head and neck tumors tend to remain localized to local or regional sites, and such tumors may recur repeatedly at the original site following treatment with surgery, external beam radiation, systemic drugs, or a combination of such treatments. Side effects associated with external beam radiotherapy include mucositis, stomatitis, permanent damage to the salivary tissues, and sometimes osteonecrosis of bones exposed to the X-rays. Many head and neck cancer patients fail local radiation therapy, with or without the addition of drugs, and thus have few treatment options. Advanced head and neck tumors eventually may metastasize to distant sites such as the lung, liver and bone. Most patients with advanced head and neck cancers die from bleeding or infections associated with recurrent and progressive cancer and the treatments used to treat such malignancies.

The present invention provides methods by which to deliver Auger electron-mediated radiotherapy, for example using $^{125}$IUDR, to locally-advanced head and neck cancers that have not yet metastasized to distant tissues. The present invention provides methods by which to deliver Auger electron-mediated radiotherapy into the treatment field using an infusible liquid vehicle that penetrates sub-mucosal tissues by the force of bulk flow.

The present invention may be used in patients who have had partial or complete surgical resection of their head and neck cancer. Alternatively, the present invention may be used in patients who have inoperable head and neck cancers. The liquid vehicle delivers $^{125}$IUDR to normal and malignant cells within the treatment field. Once in the treatment field, the $^{125}$IUDR kills those cells that are engaged in DNA synthesis and it spares the cells that are not engaged in DNA synthesis. Within the sub-mucosal treatment field, which is usually located at a distance from the site of origin, DNA synthesis occurs predominantly in the malignant cells and the blood vascular cells that are associated with the malignant cells. The present invention makes use of a liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating target cells within the sub-mucosal treatment field.

The sub-mucosal treatment field is essentially the same region that would be treated with external beam radiation. The 3-dimensional treatment field is mapped using pre-operative CT and/or MRI. The procedure for implanting the catheters into the treatment field varies depending upon the site of the tumor. In some cases, catheters may be implanted using conventional surgical approaches. In other cases, catheters may be implanted using video-assisted endoscopic techniques. Carcinous tissues tend to have a white or light tan color and a more firm texture than the uninvolved tissues within the region. Usually multiple catheters are introduced into the treatment field. A range of catheter sizes may be used; in general, 14-31 gauge catheters are well suited for this method. The catheter(s) are preferably spaced closely enough together that the distance between them is no greater than about twice the distance over which the bioactive agent can therapeutically penetrate the tissue. The proximal catheter(s) converge upon a manifold that is connected to a tube, which leads to a digitally programmable pump system equipped with a reservoir. The entire system may be surgically implanted beneath the skin.

The pump and reservoir system, usually located under the skin of the abdomen, may be filled weekly or biweekly with a solution of $^{125}$IUDR that is introduced transcutaneously via a portal leading into the reservoir. A range of $^{125}$IUDR concentrations may be used; in general, the concentration of $^{125}$IUDR is between 100 pM and 500 nM. The pump is usually programmed to infuse the $^{125}$IUDR solution at a flow rate greater than 0.5 μl/min per catheter, as needed to generate bulk flow in the target tissues. A variety of treatment schedules may be used including continuous infusion or one of a variety of intermittent schedules. A preferred schedule of administration is 6 hours of infusion (ON) followed by 6 hours without infusion (OFF).

The use of a liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within the sub-mucosal treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons or proton beams that pass through the tissues in and around the treatment field. This is a new form of radiotherapy for the treatment of cancers of the head and neck region.

In the treatment of brain tumors, pancreatic cancers, prostate cancers, head and neck cancers, and other types of locally advanced solid tumors, an alternating schedule, such as 6 hours ON/6 hours OFF, may be used for weeks or months to eliminate any cell in the treatment field that initiates DNA synthesis during the treatment period. The optimal duration of treatment will vary depending upon the kinetics of cancer cell replication in each tumor type. Normal and malignant mammalian cells require a minimum of 8 hours to complete S-phase of the cell cycle, i.e. cells need at least 8 hours to replicate their chromosomes. Therefore, the use of a repeating 6 hours ON/6 hours OFF cycle prevents any cell from completing a round of DNA synthesis without being exposed for some time to the liquid radiotherapy solution. The use of 6 hour OFF gaps also minimizes the total daily volume of infusate required to expose the treatment field, and thereby reduces the volume requirements of the reservoir.
The use of a liquid vehicle to deliver Auger electron-mediated radiotherapy to the replicating cells within the treatment field is distinct from currently available methods of radiotherapy, which make use of gamma photons, proton beams or beta electrons that penetrate the tissues in and around the treatment field. Currently available radiotherapy methods involve the ionization of water molecules throughout the path of the radiation beam as it penetrates the tissues en route to the intended treatment field. Ionization of water produces free radicals, such as hydroxyl ions and superoxide ions, throughout the path of the radiation. The free radicals mediate the therapeutic and toxic effects of such radiation by damaging DNA and other macromolecules in the cells throughout the path of radiation.

The present invention does not use radiation beams to penetrate the tissues, but rather uses a liquid vehicle to penetrate the tissues, and thereby deliver the radiation to the target cells. Furthermore, the present invention does not involve water ionization or free radical intermediates, which indirectly damage the DNA of the target cells. The present invention uses short range Auger electrons that directly destroy the DNA of the target cells. The present inventive method combines an infusible liquid vehicle and short range electrons capable of destroying any replicating target cells in the treatment field. This is a new form of radiotherapy for the treatment of malignant gliomas such as glioblastoma multiforme; a variety of brainstem tumors; locally advanced pancreatic cancer; early stage and locally advanced prostate cancer; and locally advanced cancers of the head and neck region.

A method of treating cancer, comprising administering via high-flow pressurized microinfusion a bioactive agent comprising an Auger-electron-emitting radionuclide or an analog or prodrug thereof to a volume of tissue comprising cancerous cells within the body tissue of a patient, the method comprising:

(a) disposing at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel; then,
(b) delivering under a pressure to the tissue through each catheter a solution or suspension comprising the bioactive agent, wherein the pressure is sufficient to maintain a flow rate of the solution or suspension into the tissue of at least 0.5 µl/min, for a period of time.

2. The method of claim 1 wherein the Auger-electron emitting radionuclide or analog comprises 71Br, 80mBr, 124I, 125I, or 211At.

3. The method of claim 1 wherein the radionuclide or analog comprises 5-[123I]-iodouridine 2'-deoxyribonucleoside, 5-[124I]-iodouridine 2'-deoxyribonucleoside, 5-[125I]-iodouridine 2'-deoxyribonucleoside, 5-[127I]-bromouridine 2'-deoxyribonucleoside, 5-[80mBr]-bromouridine 2'-deoxyribonucleoside, 8-[123I]-iododeoxadine 2'-deoxyribonucleoside, 8-[124I]-iododeoxadine 2'-deoxyribonucleoside, 8-[125I]-iododeoxadine 2'-deoxyribonucleoside, 5-[127I]-bromodeoxadine 2'-deoxyribonucleoside, 5-[80mBr]-bromodeoxadine 2'-deoxyribonucleoside or 5-[211At] astaurourdine 2'-deoxyribonucleoside.

4. The method of claim 1 wherein the bioactive agent comprises an Auger-electron-emitting nucleoside prodrug.

5. The method of claim 4 wherein the prodrug comprises a 3'- or 5'-phosphate or carboxylate ester of a deoxyriboyl or ribosyl moiety of the radionuclide.

6. The method of claim 1 wherein in response to the delivering under pressure of the solution or suspension through each catheter, a spatial pressure gradient exists within the tissue and the solution permeates the tissue in response to the pressure gradient.

7. The method of claim 1 wherein delivering under pressure comprises a temporal pressure profile of a solution pressure vs. time.

8. The method of claim 7 wherein the temporal pressure profile comprises a linear increase or decrease in pressure over time.

9. The method of claim 7 wherein the temporal pressure profile comprises a constant pressure over time.

10. The method of claim 7 wherein the temporal pressure profile comprises a stepwise increase or decrease in pressure over time.

11. The method of claim 7 wherein the temporal pressure profile comprises an exponential increase or decrease in pressure over time.

12. The method of claim 7 wherein the temporal pressure profile comprises a sinusoidal variation in pressure over time.

13. The method of claim 7 wherein the temporal pressure profile comprises any combination of constant, linear, stepwise, exponential, or sinusoidal pressure profile components.

14. The method of claim 7 wherein the temporal pressure profile is created using a system comprising a digitally controlled pump.

15. The method of claim 1 wherein the tissue comprises brain, head or neck tissues, esophagus, pancreas, intestines, bladder, ovary or prostate gland tissue or any tissue that is invaded by cancer cells.

16. The method of claim 1 wherein the cancerous cells comprise glioblastoma multiforme cells.

17. The method of claim 1 wherein the solution or suspension further comprises an emulsion, a liposome, a plurality of microparticles or nanoparticles, or any combination thereof.

18. The method of claim 1 wherein a concentration of the Auger-electron-emitting radionuclide or analog or prodrug thereof in the solution or suspension is about 1 micromolar to about 1 millimolar.

19. The method of claim 1 wherein the cancer is a brain cancer and the period of time is at least one hour.

20. The method of claim 1 wherein the period of time is about one week to about one year.

21. The method of claim 1 wherein the solution or suspension is delivered under pressure to the tissue continuously.

22. The method of claim 1 wherein the solution or suspension is delivered under pressure to the tissue intermittently.

23. The method of claim 1 wherein the at least one catheter is one catheter.

24. The method of claim 1 wherein the at least one catheter is two or more catheters.

25. The method of claim 1 wherein the cancerous cells are cells of an locally advanced stage solid tumor.

26. The method of claim 1 wherein the cancerous cells are cells of tumor processes penetrating volumes of non-cancerous tissue.

27. The method of claim 1 further comprising administration of a second anticancer agent.

28. The method of claim 1 further comprising administration of a medicament other than an anticancer agent.

29. The method of claim 1 further comprising, following step (b), delivering under pressure a physiologically-compatible solution that does not contain the Auger-electron-emitting radionuclide.
30. The method of claim 1, further comprising, prior to step (a), selecting a patient afflicted with an advanced stage solid tumor or a cancer wherein tumor processes have invaded surrounding non-cancerous tissue; then disposing the at least one catheter within the tissue in proximity to the cancerous cells and not within a blood vessel then delivering the solution or suspension comprising the bioactive agent under pressure to the tissue for the period of time.

31. A method of assembly of a system adapted for practice of the method of claim 1, comprising connecting a source of a pressurized liquid to a catheter adapted for intratissue delivery of a liquid under pressure, wherein the pressurized liquid comprises the Auger-electron emitting radionucleoside or analog thereof.