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(54) Title: BIODEGRADABLE SPINAL FIDUCIAL IMPLANT AND METHOD

(57) Abstract: A biodegradable fiducial implant for use in establishing a common, stable frame of reference for preoperative and operative spinal images of a patient is disclosed. The implant includes a rigid, biodegradable body having a tapered insertion portion for inserting the implant in contact with a vertebra in the patient, where at least a portion of the implant being formed of a radio-opaque material. Also disclosed is a fiducial composition for use in generating a scan image of an internal target region of a patient.

BIODEGRADABLE SPINAL FIDUCIAL IMPLANT AND METHOD

Field of the Invention

The present invention relates to a spinal fiducial implant, and more specifically to a biodegradable fiducial implant that is capable of being stably implanted or injected in a spinal target region for use during minimally invasive imaging procedures.

Background of the Invention

A variety of diagnostic imaging techniques are available for providing high fidelity views of the human body. Non-invasive imaging systems which provide cross-section views of anatomical structure include plain view X-ray imagers, computerized axial tomography X-ray (CAT scanning) imagers, magnetic resonance (MR) imagers, positron emission tomography (PET) scanners, and ultrasound scanners

In these imaging techniques, each set of images has a discrete, unique orientation since the images obtained will be depend on the patient's position within the imaging device. Images formed from the same imaging modality at different times and images formed at essentially the same time, but from different imaging modalities, cannot accurately be compared on a point-by-point basis. To address this problem, fiducial implants are attached to, or injected into the patient in the scanned region to provide a reference frame for comparing images formed at different times and for comparing images formed from different modalities.

In addition, the use of 2D and 3D images of anatomical structures are becoming widely used in the planning of surgical procedures and during the real time performance of surgical procedures. It is crucial to establish a link between the preoperative images and the intraoperative space in order to reproduce the surgical planning accurately.

In computer assisted orthopaedic surgery, a registration process uses fiducial implants to determine the geometric correspondence between the surgical plan and the patient's bones (e.g., see U.S. Patent Nos. 5,230,338;

5,682,886; and *Clin. Orthop.* 354:49-56, 1998). Fiducial markers such as screws (U.S. Patent no. 5,230,338), reference pins (U.S. Patent no 5,772,594) and wires (Simon et al., *Clin. Orthop.* 354:17-27, 1998) have been described for use in cranial and orthopaedic applications. For orthopedic and spinal surgery, the fiducials primarily have been used in "open" surgical procedures in which the bone is exposed during surgery and the fiducials are attached to the exposed bone surfaces.

Minimally invasive surgery is a preferred surgical method. As minimally invasive surgical procedures become more widely used, there is a need for suitable registration methods. In particular, there is a need for fiducial implants which can be implanted or injected within or near the subsurface target site with minimal disruption or destruction of patient tissue, which will remain stably fixed at precise body positions from the time that preoperative images are taken to the time of the intraoperative procedures, and which can be biodegradable, thus eliminating the need for removal following surgery. These needs are particularly important in spinal surgery where the bone surfaces are located deep beneath muscle layers, and where the vertebrae of the spine are free to move during surgery.

Summary of the Invention

In one aspect, the invention includes a fiducial implant for use in establishing a common, stable frame of reference for preoperative and operative spinal images of a patient. The implant is formed of a rigid, biodegradable body having a tapered insertion portion for inserting the implant in contact with a vertebra in the patient. At least a portion of the implant is formed of a radio-opaque material.

In various embodiments, the tapered insertion portion has a conical shape, and the tapered insertion portion is threaded, for threaded attachment to a vertebra, where the body has a head portion provided with structure for engaging an attachment tool. The implant has a preferred length dimension between 3-8 mm, and a width dimension between 1-5 mm.

In a related aspect, the invention includes an improvement in a method for establishing a common, stable frame of reference for preoperative and

operative spinal images of the patient. The method includes implanting at selected locations in a target region, a plurality of image-opaque fiducial implants of the type described above.

In one embodiment, the implanting step is done by making an incision of less than 1 cm in the patient, through tissue surrounded the target vertebra, and inserting the implant through the incision until it is in contact the vertebra.

In another aspect, the implant is dimensioned to be moved within a needle, and the implanting step includes puncturing the tissue surrounding such vertebra with the needle, forcing the implant in the needle against the vertebra, and withdrawing the needle from the implantation site.

In still another aspect, the invention includes a fiducial composition for use in generating a scan image of an internal target region of a patient. The composition includes a detectable agent which is attached to a biodegradable carrier, where the carrier is adherent to the target region, and the composition includes sufficient detectable agent such that it is viewable in said scan image.

In various embodiments, the composition is effective to solidify from a liquid upon injection into the patient, the carrier is calcium phosphate, collagen, gelatin, fibrin, and fibrinogen, and the detectable agent is a biocompatible metal, metal alloy, or amalgam.

These and other objects and features of the invention will be more fully appreciated when the following detailed description of the invention is read in conjunction with the accompanying drawings.

Brief Description of the Drawings

Fig. 1 illustrates a spine have a plurality of biodegradable fiducial markers applied thereto;

Fig. 2 is a side view of one preferred embodiment of a biodegradable fiducial implant of the invention;

FIG. 3 is a side view of another embodiment of a biodegradable fiducial implant of the invention;

FIG. 4 is a side view of an embodiment of the invention adapted for threaded attachment to vertebra bone;

Figs. 5A and 5B illustrate of steps in practicing one embodiment of the

method of the invention; and

Figs. 6A and 6B illustrate steps in practicing the method of the invention by implant injection.

Detailed Description of the Invention

Fig. 1 shows a region 10 of a patient's spine containing three vertebrae 12, 14, 16. The region shown represents a surgical target area or region intended for spinal surgery. During surgery, it is important for the surgeon to be able to view subsurface target structures, to maximize the surgical operation steps, and minimize the risk of cutting or damaging critical nerves or vascular structures. To this end, the surgeon would like to be able to "see" hidden or subsurface structures in the region of the target. At the same time, the surgeon wishes to minimize the amount of cutting of tissue that is interposed between the surgeon and the spinal region of interest.

To optimize these aims, the surgeon can choose to perform the operation in a setting where preoperative scan images may be used to create perspective or other views of subsurface structures during the operation. The subsurface structures may be viewed, for example, from the position and orientation of a surgical tool, allowing the user to "see" what is immediately ahead of or adjacent the tip of the surgical tool, without the need to cut away any musculature or other tissue other than what is required to insert the tip of the tool to the target site. This capability, it will be appreciated, greatly minimizes the invasiveness of the surgical procedure, while providing the surgeon with an accurate view of the surgical target.

Image-guided surgery of this type has three basic requirements:

1. Preoperative scan data from the patient target site must be obtained. This is typically CT or MRI data, but may include ultrasonic or other imaging techniques.

2. During surgery, the imaging data must be placed in the frame of reference of the patient. In other words, in order to display meaningful images to the surgeon, the computer used in generating the images must know the position of the images with respect to the intraoperative position of the patient.

3. The image-guidance system must be able to place the surgical

instrument in the frame of reference of the patient, so that the system computer can generate images with respect to the position and orientation of the surgical tool.

These requirements can be met by injecting or placing scan-detectable fiducials on or in a patient target region prior to collecting the scan data. The scan data then includes images of the fiducials that can then be used to reconstruct scan image in the frame of reference of the fiducials. During surgery, the same fiducials at the same positions can be used to establish a "patient" frame of reference. The latter can be established, e.g., by intraoperative fluoroscopic imaging, to determine the coordinates of the fiducials with respect to the patient, surgical bed, or some other fixed object in the surgical theater. Once this patient frame of reference is established, the surgical tool can be placed in the same reference frame, to allow the system to generate subsurface target images as seen from a desired vantage, e.g., the tip of a surgical tool.

In surgery involving the skull, the requirement for stability of fiducial position can be achieved by securing the fiducials to the head or skull region. In spinal surgery, the problem is more difficult, because of the more difficult accessibility of vertebrae and the ability of adjacent vertebrae to move with respect to one another.

The present invention addresses the problem of stable placement of fiducials in a target region of the spine with minimal disruption or invasion of surrounding tissue, e.g., the musculature and vasculature surrounding the spine.

With continued reference to Fig. 1, the surgical target area is shown with four fiducial implants, such as implants 20 placed on two of the vertebra at the target site. These implants are imaged during image scan collection and during surgery, and are used to establish a patient frame of reference, by which a surgical tool and pre-operative scan data can be placed in a common, precisely known patient frame of reference.

Figs. 2-4 show three exemplary embodiments of rigid, biodegradable implants constructed in accordance with the invention, all in side view. The biodegradable implant shown in Fig. 2, indicated at 20, includes a tapered

conical insertion portion 22 terminating at a lead tip 24 and a rounded head portion 26, the two portions forming an implant body. The implant body has a preferred length dimension of between 3-10 mm, and a preferred width dimension between 2-5 mm.

The implant is formed as a unitary piece from a biodegradable, radio-opaque material, employing rigid biocompatable, biodegradable materials, according to methods known in the art, e.g., U.S. Patent Nos. 6,027,744, 5,921,979, 5,645,592, 5,443,495, and 4,735,804. For example, the biodegradable material may be a biodegradable polymer, such as polylactic acid, polyglycolic acid, or a mixed polylactic/polyglycolic polymer. The radio-opaque agent may be included in the polymerization mixture or coupled, e.g., covalently to the polymer implant after the implant is formed and molded, as detailed below. Alternatively, the implant may be formed of a biocompatable metal, e.g., iron, which will can dissolve on extended contact with aqueous medium, e.g. body fluids.

Fig. 3 shows a rigid, biodegradable implant 30 constructed according to another embodiment of the invention. The implant includes a tapered conical insertion portion 32 terminating at a lead tip 34 and a conical head portion with a rounded tip region 38. The dimensions and construction of the biodegradable implant are similar to those described with respect to implant 20.

Fig. 4 shows a rigid, biodegradable implant 42 constructed according to yet another embodiment of the invention. As above, the implant includes a tapered conical insertion portion 44 terminating at a tip 48, and a conical rounded head portion 50. The insertion portion is threaded, as at 46, and the head portion is provided with an engagement slot, as at 52, to allow the surgeon to attach the implant to the bone by twisting, screw-like. The construction and dimensions of the implant are similar to those described above for implant 20.

Figs. 5A and 5B illustrate steps in the use of the implant of the invention, in accordance with the method of the invention. The figures show a portion of vertebral bone 60 and a surrounding musculature 62 attached to the bone. The purpose of the method, and implant construction, is to allow stable attachment of an implant at a selected position on a vertebra, with a minimum of

destruction to the surrounding musculature and/or vasculature.

With reference to Fig 5A, initially the surgeon makes a small incision 64 in the surrounding tissue. This incision is preferably no wider than 1 cm, and preferably no wider than the width of the implant, and can be made with a scalpel or the like having a selected blade width.

To place an implant, such as implant 20, at the target site, the surgeon places the implant into the incision and moves it through the incision until the lower tip of the implant is pressed against the vertebra surface, as illustrated in Fig. 5B. The surgeon may employ a grasping or guiding tool to help orient the implant during the placement process. For example, the rounded implant head may include a circular channel for receiving the cylindrical tip of a guiding tool.

It will be appreciated from Fig. 5B that with the implant positioned against the bone, the surrounding tissue, which has been spread to receive the implant, closes over the implant to hold it securely in place, anchored at its tip against the bone surface. Where the implant includes threaded structure, the implant may be twisted into a preformed hole in the bone, for additional anchoring to the bone.

Figs. 6A and 6B illustrates steps in placement of the implants, in accordance with another embodiment of the invention. As above, the figures show a portion of vertebral bone 70 and a surrounding musculature 72 attached to the bone. With reference to Fig 6A, initially the surgeon loads a needle 74, typically one having in inner diameter of about 0.5 -1.5 mm, with a biodegradable implant 76 dimensioned for axial movement within the needle. As seen, the implant has a rod-like body with a "lower" pointed insertion portion 78.

The loaded needle is then inserted through the musculature surrounded the target bone site until the tip of the needle is against the bone. The implant is then pushed out through the needle, e.g., by a separate plunger or pusher wire (not shown) until the tip of the implant is forced against the bone. The needle is now carefully withdrawn, preferably with the pusher wire held in place to hold the implant against the bone.

Following this, and after removal of the needle and pusher wire, the tissue surrounding the implant closes around and over the implant, encasing it

stably at the target site, as illustrated in Fig. 6B. After the preoperative and intraoperative procedures that rely on the implant, the implant remains in place where it will biodegrade.

From the foregoing, it will be appreciated how various objects and features of the invention for a rigid, biodegradable implant are met. The implant of the invention can be placed at a target surgical site in the spinal region by insertion through a small, relatively non-invasive surgical incision or needle puncture. When placed at the target site, an implant is stably fixed at the site by virtue of its contact with or against a bone surface, and its envelopment by surrounding tissue. The implant will biodegrade at the site, typically within 1-4 weeks.

In another aspect, the invention includes an implant composition for use image-guided surgical procedures for the spine. The composition employs a substantially uniform dispersion of a contrast agent coupled to a physiologically acceptable carrier, particularly a protein such as collagen, fibrinogen, or a derivative thereof, or other high molecular weight physiologically acceptable biodegradable composition, dispersed in a minor amount of a physiologically acceptable aqueous medium. The resulting amorphous mass is injected into the body at a suitable location, e.g., bone surface, or other organ surface.

The preferred carrier is flowable for injection, but provides for stable placement, once injected into the tissue. That is, once injected, the preferred carrier adheres to the tissue and does not migrate significantly. After injection, the contrast agent remains at the site of injection during requisite scanning procedures.

The subject compositions are amorphous, injectable and viscous, so as to substantially retain a localized position without significant flow from the site of administration. The compositions can flow under moderate pressure, but will not move significantly after being positioned at a particular site.

The carrier material can be comprised of a proteinaceous material, examples of which include collagen, fibrin, gelatin, crosslinked gelatins, fibrinogen, and elastin. Proteinaceous compositions having at least about 5 weight percent, preferably at least about 10 weight percent, and up to 50 weight percent or more, are of particular interest. Other examples of carrier

materials include carbohydrates, resorbable polymers such as polylactic acid, and glycolytic acid.

Preferably, the composition will be comprised of a significant amount of the carrier to provide the desired composition characteristics. The carrier may be comprised of individual or in combination peptides or proteins, e.g., structural proteins such as collagen and fibrinogen, or albumin or other protein which provides for stable placement, or combinations thereof. Of particular interest is collagen, fibrinogen or derivative thereof.

In addition to the matrix material will be one or more contrast agents, and a physiologically acceptable aqueous medium in which the proteinaceous composition is dispersed and the drug may be dissolved, dispersed, or complexed with the collagen. Other materials are preferably present to enhance the beneficial properties of the subject composition.

For convenience, a proteinaceous carrier will be described hereinbelow, by way of example only, it being understood that other carrier materials may also be similarly used.

The proteinaceous, particularly collagenous or fibrinogen-containing, material which is used may be derived from any mammalian host source, such as bovine, porcine or human, or may be prepared, as available, by other techniques, e.g. recombinant DNA techniques. The collagen employed may be natural collagen or may be modified, such as tropocollagen, atropocollagen, or the like.

As already indicated, the ratio of dry materials in the composition may vary widely. However, the amount of protein matrix material will usually be not less than 30% and not greater than about 95%, generally ranging from about from 40% to 90%, more usually ranging from about 50% to 90% by weight. Of this, preferably 10 to 100% will be collagen and/or fibrinogen. The contrast agent(s) will normally be a liquid or solid, or provided in solid form and generally range from at least about 0.1% by weight to up to about 50% by weight, more usually being from about 1% to 50% by weight, generally being from about 1% to 45% by weight of the proteinaceous material.

Other ancillary additives or agents will vary in total amount from about 0.005 to 15, usually from about 0.01 to 10 weight percent of the dry weight of

the total composition.

The composition is uniformly dispersed in a physiologically acceptable aqueous medium, such as saline, phosphate buffered saline, distilled water, etc. The aqueous medium will be sufficient to provide for an amorphous dispersion capable of flowing under mild pressure. The concentration of protein in the aqueous medium will range from about 5 to 75 mg/ml. The concentration will vary depending upon the nature of the contrast agent, the nature of the matrix material, the presence of other materials, and the like.

In addition to the major components, a number of minor components may also be included for a variety of purposes. These agents will for the most part impart properties which protect the stability of the composition, control the pH, or the like. Illustrative agents include phosphate or acetate buffers, methyl or propyl paraben, polyethylene glycols, etc. These agents generally will be present in less than about 2 weight percent of the total composition, usually less than about 1 weight percent, and individually may vary from about 0.001 weight percent to about 1 weight percent.

Collagen is the major fibrous protein of many animals and may be extracted from many parts of the human or animal body. Fibrillar collagen is a preferred carrier material for use in the present invention as are materials which comprise a substantial proportion of it. Useful carrier material may also be formed by incorporating collagen fibres into or onto a suitable supporting material. An example of a supporting material is natural or synthetic calcium phosphates which substances may usefully form part of the materials of this invention.

Collagen offers a number of advantages in the present application. For one, it is very persistent-that is, it is not prone to migration or dispersal after injection. It is very biocompatible and has been widely used in medical implants.

A preferred form of collagen for use as a carrier in the invention is atelocollagen. This is formed by enzymic removal of an antigenic telopeptide from collagen, such as by pepsin digestion. Crosslinked atelocollagen is available from Koken Co.., Ltd., Tokyo, Japan and is described in U.S. Pat. No. 5,314,874.

The fiducial marker, after injection, will preferably not spread or migrate through the surrounding tissues. It is important that the fiducial markers of the invention remain bound at the site of attachment during the imaging process and for subsequent scans, if needed. This characteristic is met by using collagen solutions which precipitate at body temperature, thus leading to the formation of fibers which remain at the injection site (see U.S. Pat. No. 3,949,073). An advantage of using collagen is its bioadhesive property (U.S. Patent No. 5,660,692) which causes the fiducial markers to adhere to tissue at the site of injection.

In another embodiment of the invention, the carrier comprises microcapsules of atelocollagen or a mixture of atelocollagen and a polysaccharide, particularly glycosaminoglycan as described in U.S. Patent No. 5,568,593. The process of preparing the microcapsules is described in U.S. Pat. No. 5,395,620.

The collagen can be modified by crosslinking agents which can increase the stability and decrease the antigenicity of the carrier material of the invention.

Examples of crosslinking agents include glutaraldehyde, carbodiimide, polyepoxy compounds (e.g., as described in U.S. Pat. No. 5,314,874), photoactivatable chemical crosslinkers (e.g., as described in U.S. Pat. No. 5,660,692), and polyepoxy compounds (U.S. Pat. No. 5,314,874).

Crosslinking agents have the further advantage of minimizing inflammation due to the presence of the carrier.

Cross-links can be introduced into the carrier by using a crosslinking agent such as glutaraldehyde, acid dichloride, acid anhydride or a di- or polybasic carboxylic acid, as described in U.S. Pat. No. 5,658,593. The degradation rate of the fiducial marker can be modulated by varying the amount of crosslinks in the carrier. The desired degradation rate will depend upon when scan images are needed. Preferably, the fiducial marker will not change shape between scans. Multiple scans can be taken over the course of radiation, chemotherapeutic or surgical treatment. Thus, the fiducial marker can be designed to persist, e.g., for one week to one year, depending upon the treatment and the scanning modality required.

In addition to the carrier material will be one or more contrast agents coupled to the carrier. The contrast agent can be a solid, liquid or gas which is readily discernable with the particular type of imaging used.

For example, the fiducial marker can be used in Magnetic Resonance Imaging (MRI). MRI employs a magnetic field, filed gradients and radiofrequency energy to excite protons and thereby make an image of the mobile photons in water and fat. Suitable MRI contrast agents include barium and iodine compounds, gadolinium-DTPA. Also suitable are chelating compounds in combination with paramagnetic ions. For example, the wide variety of polyphosphorylated aliphatic and alicyclic compounds can be employed in combination with paramagnetic ions, e.g., as described in U.S. Pat. No. 5,885,549. Other chelating agents include porphyrazine compounds (U.S. Pat. No. 5,912,341), 1,4,7,10-tetraazacyclododecane and its derivatives, porphyrins, porphyrinoid compounds (U.S. Pat. No. 5,886,173), and polyaza compounds (U.S. Pat. No. 5,874,573).

Contrast agents for MRI include magnetic compounds, e.g. paramagnetic ions, iron, manganese, gadolinium, lanthanides, organic paramagnetic moieties and superparamagnetic compounds, e.g., iron oxide colloids, ferrite colloids, etc.

Suitable paramagnetic ions include, but are not limited to, compounds comprising transition, lanthanide and actinide elements, and any of the suitable paramagnetic ions, and any combinations thereof, are intended to be within the scope of the present invention. Preferable of such elements are Gd(III), Mn(II), Cu(II), Cr(III), Fe(II), Fe(III), Co(II), Er(II), Ni(II), Eu(III), Yb(III), Lu(III) and Dy(III). More preferably, the elements are Fe(III), Gd(III), Mn(II), Cu(II), Cr(III), Yb(III), Dy(III), Fe(III) and Mn(II).

Combinations of paramagnetic ions are within the scope of the present invention. Choice of appropriate combinations of paramagnetic ions can increase the ultimate relaxivity and contrast enhancement of the contrast media of the present invention.

The fiducial marker of the instant invention can be used in Computed tomography (CT). CT is a diagnostic imaging technique which measures, in its imaging process, the radiodensity of matter. Radiodensity of matter is typically

expressed in Hounsefield Units (HU). Hounsefield Units are a measure of the relative absorption of computed tomography X-rays by matter and is directly proportional to electron density. Water has arbitrarily been assigned a value of 0 HU, air a value of -1000 HU, and dense cortical bone a value of 1000 HU.

Contrast agents for CT and other X-ray based imaging methods include metal ions which are able to absorb adequate amounts of X-rays. In general, the contrast agents of the present invention have a higher density than bone. These metal ions are generally referred to as radiopaque. Suitable elements for use as the radiopaque metal ion include lead, bismuth, gadolinium, dysprosium, holmium and praeseodymium. Other contrast agents include iodine and barium.

A commonly used contrast agent for computed tomography is barium sulfate. Barium sulfate increases electron density in certain regions of the body, and is classified as a "positive contrast agent."

In the instant invention, barium sulfate, or other contrast agent, can be contained within microspheres. The microspheres are formed from, for example, a biocompatible lipid or polymer. In preferred embodiments, the biocompatible lipid comprises a phospholipid which is in the form of a lipid bilayer.

Another example of a contrast agent for use in the present invention comprises stabilized gas and gaseous precursor filled microspheres, wherein the gas may be, for example, air or nitrogen, but may also be derived from a gaseous precursor, for example, perfluoropentane (e.g., as described in U.S. Pat. No. 5,874,062).

As described hereinbelow, methods for attaching microspheres to protein carriers are well known in the art. Nonlimiting examples of coupling agents include avidin/biotin, antibody/receptor, and reactive coupling compounds.

Still other examples of contrast agents include substances useful for neutron activation, such as boron. Organic compounds incorporating boron are well known and can be attached to the carrier of the instant invention.

Contrast agents for positron emission tomography include Tc99m, which can be attached to the carrier of the present invention via an antibody, such as

88BV59 Ab.

Diagnostic labels such as diagnostic radiopharmaceuticals, can be attached to the carrier of the invention. Examples of radiopharmaceuticals include 90Y, 111In, 68GA, 99mTc, 67Cu, 57Co, 131I.

The use of a radioactive isotope allows tracking the movements of the fiducial marker from outside of the body. One such procedure utilizes scintigraphy (e.g., as described in U.S. Pat. No. 5,919,934) Tomographic imaging procedures such as single photon emission computed tomography (SPECT) can also be used to improve visualization.

A wide variety of coupling agents for attaching contrast agents to the carrier of the instant invention are known. Preferred coupling agents provide a stable association such that the contrast agent will remain bound to the proteinaceous carrier for the required length of time.

In the embodiment comprising a collagen carrier, it will be recognized that collagen contains a number of available amino and hydroxy groups which may be used to bind coupling agents.

Covalent attachment is preferred, although other high affiinity interactions such as between members of specific binding pairs (e.g., antibody/antigen, avidin/biotin) can be used.

In one embodiment, the covalent bond is formed between the contrast agent and the carrier directly. For example, methods are known for binding iodine radioisotopes to proteins.

In other embodiments, a contrast agent such as a metal ion, can be complexed with a chelate or antibody, which in turn can be covalently attached to the proteinaceous carrier of the invention. Examples of organic chemicals which can form chelates with metals include polyamine chelating agents such as EDTA, DOTA, DTPA , and other compounds (e.g., as disclosed in U.S. Pat. Nos. 5,869,651; 5,871,710; 5,869,026).

The linkage of a chelating compound to a macromolecule or backbone polymer may be effected by the methods of Salutar (WO-A-90/12050) or by any of the conventional methods such as the carbodiimide method, the mixed anhydride procedure of Krejcarek et al. (see Biochemical and Biophysical Research Communications 77: 581 (1977)), the cyclic anhydride method of

Hnatowich et al. (see Science 220: 613 (1983) and elsewhere), the backbone conjugation techniques of Meares et al. (see Anal. Biochem. 142: 68 (1984) and elsewhere) and Schering (see EP-A-331616 for example) and by the use of linker molecules as described for example by Nycomed in WO-A-89/06979.

In additional embodiments, antibodies are known which bind selected metals in certain oxidation states. Other antibodies are known which bind metal-chelate complexes.

Combination is brought about by incubating the carrier material with the antibody in the presence of a coupling agent which is capable of covalently bonding with the carrier and with the antibody. Suitable coupling agents are those which are capable of bonding to the antibody without significantly reducing its biological activity. A wide variety of polyfunctional compounds may be useful.

The coupling agents used to form the preferred materials of this invention will be those which are capable of bonding to the carrier material. Examples of potentially useful coupling agents include biotin-avidin; glutaraldehyde and 1-ethyl-3(3-dimethyl-aminopropyl)carbodiimide HCl. The preferred coupling agents are those which do not produce an adverse reaction when introduced into the body in particular as part of a material according to this invention.

A particularly preferred coupling agent is that known as SATA-MHS, which involves the use of a combination of succinimide-S-acetylthioacetate (ATA) and maletmidohexanoyl-N-hydroxysuccinimde (MHS). Preferably the carrier is incubated with the SATA and the antibody with the MHS. The products of these two incubation processes are combined and allowed to react. The material is then incubated with a suitable metal, or metal-chelate complex, in order to produce a fiducial marker material.

As described hereinabove, a contrast agent can be contained within microvesicles, such as protein or lipid vesicles. Such vesicles can include chemical coupling agents (e.g. as described in U.S. Pat. No. 5,718,915) attached to or embedded within the vesicles for attachment to the carrier of the invention .

It will be recognized that more than one type of contrast agent can be

attached to the carrier of the invention so that a single fiducial marker can be used in different types of scanning modalities.

It will also be appreciated that nanoscale devices, such as signal processing means for providing an output in response to an input (e.g., see U.S. Pat. Nos. 4,793,825 and 5,868,673), can be attached to the injectable carrier of the instant invention, for placement at selected sites within a patient's body.

The invention includes kits for imaging a region of a patient. For example, kits useful for magnetic resonance imaging of a region of a patient in accordance with the present invention comprise at least one MRI contrast agent essentially irreversibly coupled to an injectable proteinaceous carrier, and can include conventional proton magnetic resonance imaging kit components (e.g., such as described in U.S. Pat. No. 4,719,098). Exemplary components include polymers, anti-oxidants, various T2 relaxation agents, osmolality raising agents, viscosity and bulking agents, and buffering agents.

Kits useful for CT imaging of a region of a patient in accordance with the present invention comprise at least one CT contrast agent essentially irreversibly coupled to an injectable proteinaceous carrier, and can include buffering agents, and antioxidants.

From the foregoing, it will be appreciated how various objects and features of the invention are met. The implant of the invention can be placed at a target surgical site in the spinal region by insertion through a small, relatively non-invasive surgical incision. When placed at the target site, an implant is stably fixed at the site by virtue of its contact with or against a bone surface, and its envelopment by surrounding tissue. The implant is biodegradable and does not need to be retrieved after a surgical procedure, further minimizing damage to the tissue near the target site.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

IT IS CLAIMED:

1. A fiducial implant for use in establishing a common, stable frame of reference for preoperative and operative spinal images of a patient, comprising

a rigid, biodegradable body having a tapered insertion portion for inserting the implant in contact with a vertebra in the patient,

at least a portion of the implant being formed of a radio-opaque material.

2. The implant of claim 1, wherein the tapered insertion portion has a conical shape.

3. The implant of claim 1, wherein the tapered insertion portion is threaded, for threaded attachment to a vertebra, and the body has a head portion provided with structure for engaging an attachment tool.

4. The implant of claim 1, which has a length dimension between 3-8 mm, and a width dimension between 1-5 mm.

5. In a method for performing image guided surgery on a spinal target region of a patient, a method for establishing a common, stable frame of reference for preoperative and operative spinal images of the patient, comprising

implanting at selected locations in a target region, a plurality of image-opaque fiducial implants, each having a rigid, biodegradable body having a tapered insertion portion for inserting the implant in contact with a vertebra in the patient, at least a portion of the implant being formed of a radio-opaque material.

6. The method of claim 5, wherein said implanting includes making an incision of less than 1 cm in the patient, through tissue surrounded such vertebra, and inserting the implant through the incision until it is in contact the vertebra.

7. The method of claim 6, wherein the implant is dimensioned to be moved within a needle, and said implanting includes puncturing the tissue surrounding such vertebra with the needle, forcing the implant in the needle against the vertebra, and withdrawing the needle from the implantation site.

8. A fiducial composition for use in generating a scan image of an internal target region of a patient, comprising

a detectable agent which is attached to a biodegradable carrier, wherein said carrier is adherent to said region, wherein said fiducial composition includes sufficient detectable agent such that said fiducial composition is viewable in said scan image.

9. The composition of claim 8 which is effective to solidify from a liquid upon injection into said patient.

10. The composition of claim 8, wherein said carrier includes a material selected from the group consisting of calcium phosphate, collagen, gelatin, fibrin, and fibrinogen.

11. The composition of claim 8, wherein said detectable agent comprises a biocompatible metal, alloy, or amalgam.

12. The composition of claim 8, wherein said detectable agent comprises iron, gold, titanium, stainless steel, or nitinol.

13. The composition of claim 8, wherein said detectable agent comprises magnetic or paramagnetic material.

14. The composition of claim 8, wherein said detectable agent comprises a radioisotope, iodine, or barium.

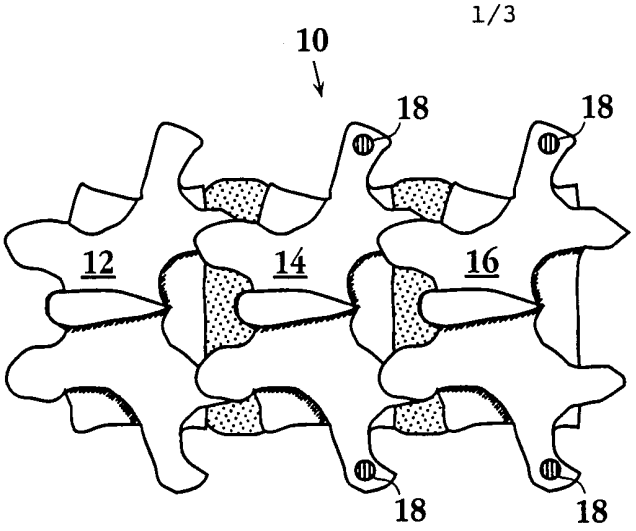

Fig. 1

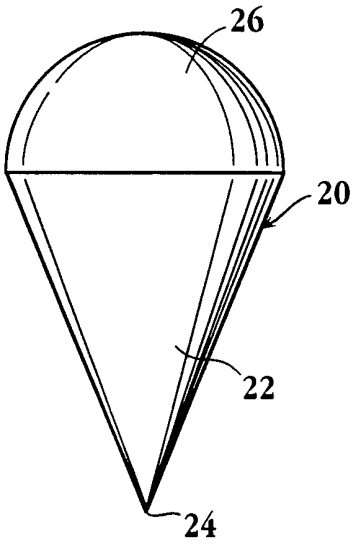

Fig. 2

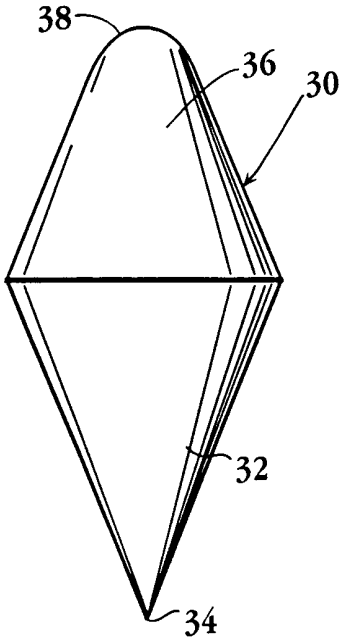

Fig. 3

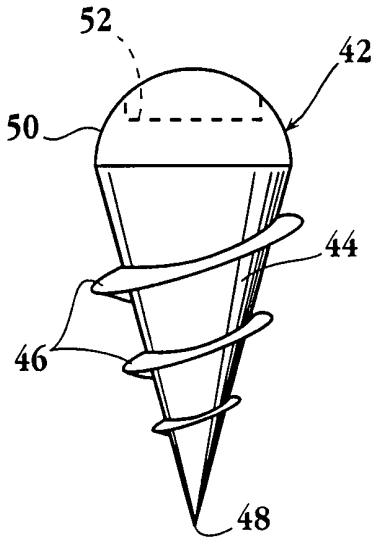

Fig. 4

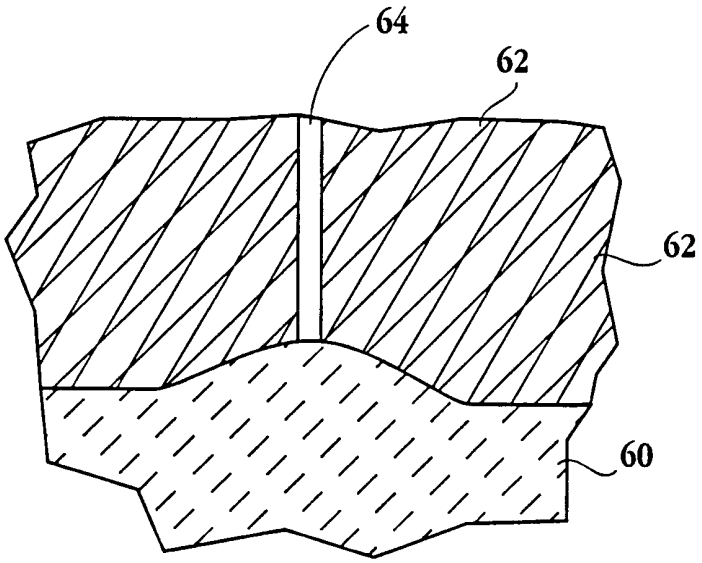

Fig. 5A

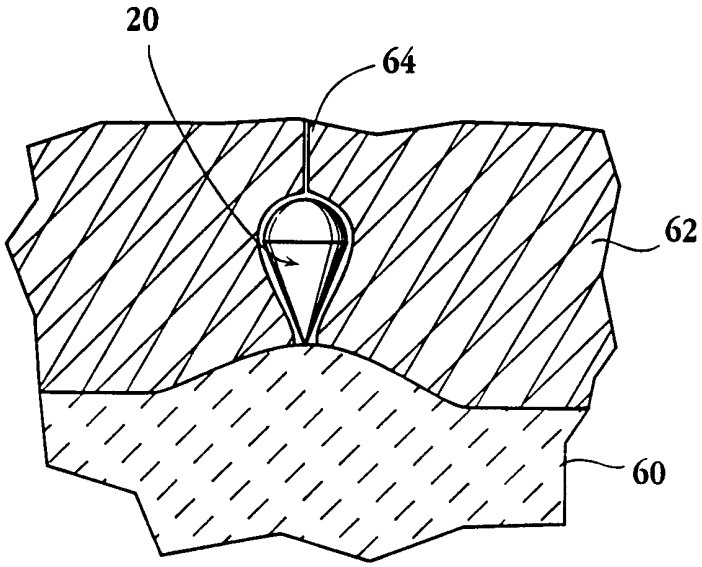

Fig. 5B

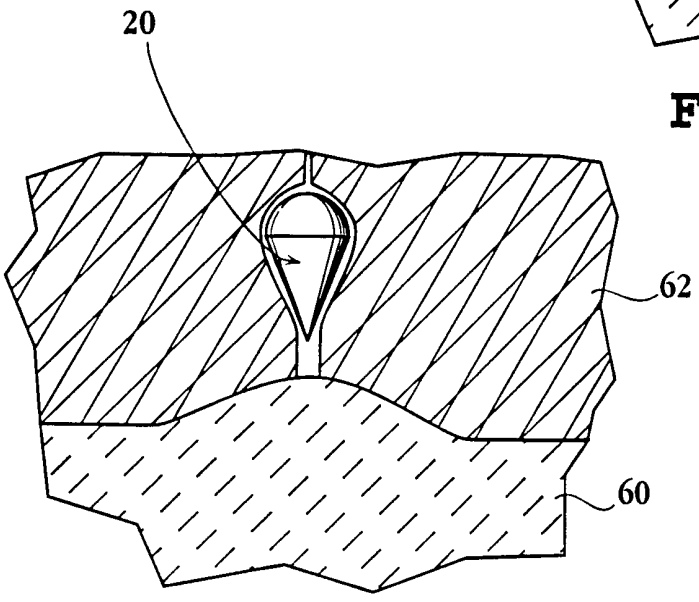

Fig. 5C

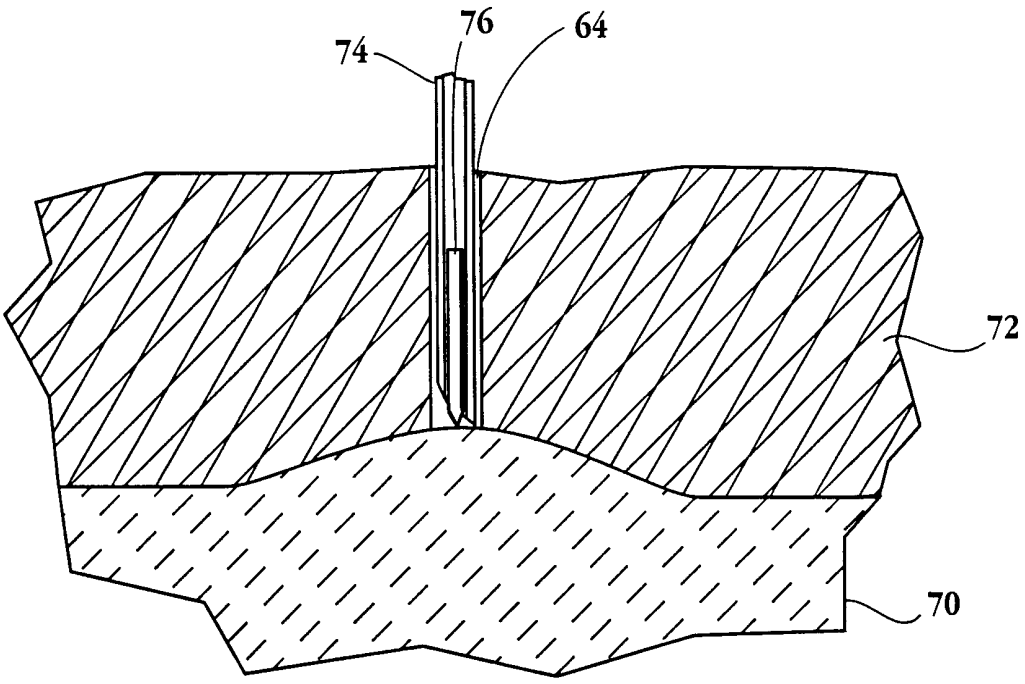

Fig. 6A

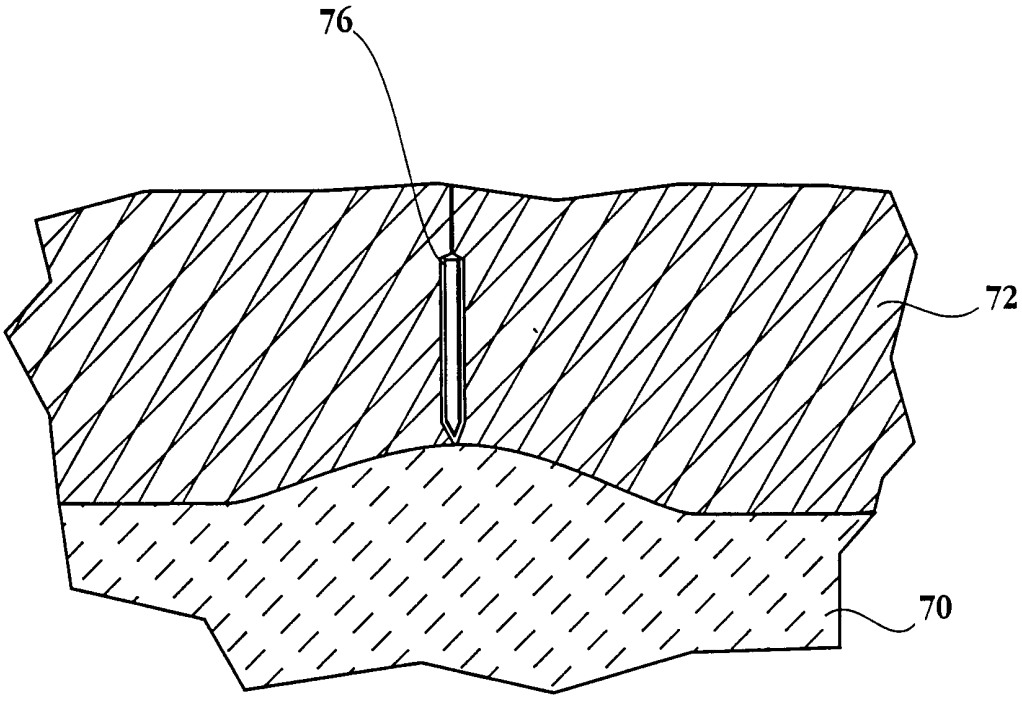

Fig. 6B