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(54) **IMAGEABLE BIOPSY SITE MARKER**

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(63) Continuation of application No. 11/258,324, filed on Oct. 25, 2005, which is a continuation of application No. 10/719,448, filed on Nov. 21, 2003, now Pat. No. 6,996,433, which is a continuation of application No. 10/684,124, filed on Oct. 10, 2003, which is a continuation of application No. 10/001,043, filed on Oct. 31, 2001, now Pat. No. 6,662,041, which is a continuation of application No. 09/343,975, filed on Jun. 30, 1999, now Pat. No. 6,347,241, which is a continuation-in-part of application No. 09/241,936, filed on Feb. 2, 1999, now Pat. No. 6,161,034.

Publication Classification

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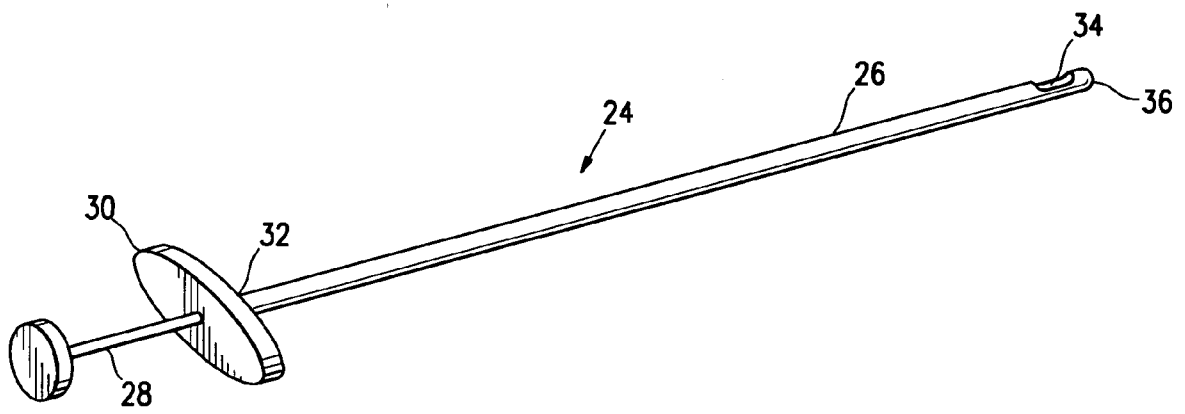
(57) **ABSTRACT**

A biopsy site marker having at least one small marker body or pellet of bioresorbable material such as gelatin, collagen, polylactic acid, polyglycolic acid which has a radiopaque object, preferably with a non-biological configuration. The at least one bioresorbable body or pellet with a radiopaque object is deposited into the biopsy site, by a delivery device that includes an elongated tubular body with a piston slidable within the tubular body. One end of the tube is placed into the biopsy site. At least one but preferably several marker bodies or pellets are deposited sequentially into the biopsy site through the tube. At least the bioresorbable materials of the detectable markers remain present in sufficient quantity to permit detection and location of the biopsy site at a first time point (e.g., 2 weeks) after introduction but clear from the biopsy site or otherwise do not interfere with imaging of tissues adjacent the biopsy site at a second time point (e.g., 5-7 months) after introduction.



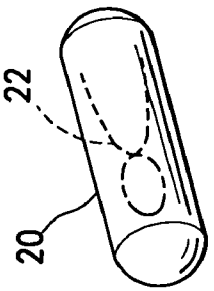


FIG. 1

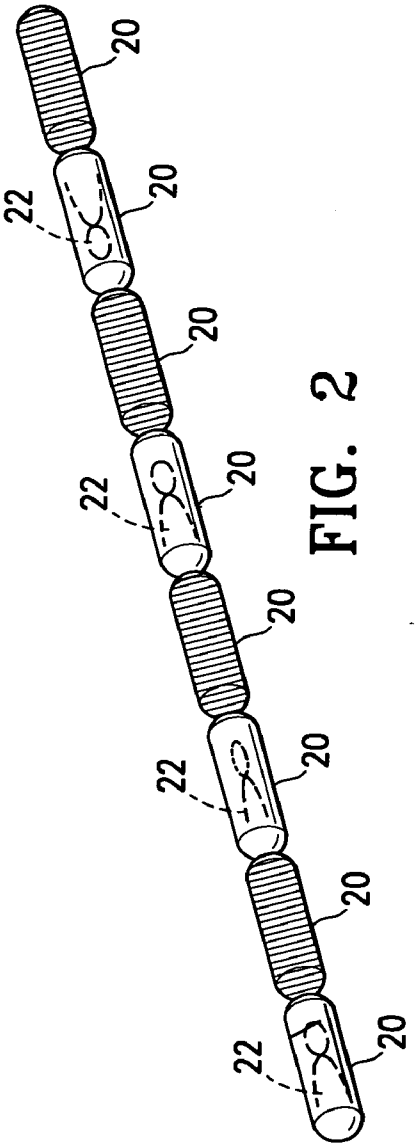


FIG. 2

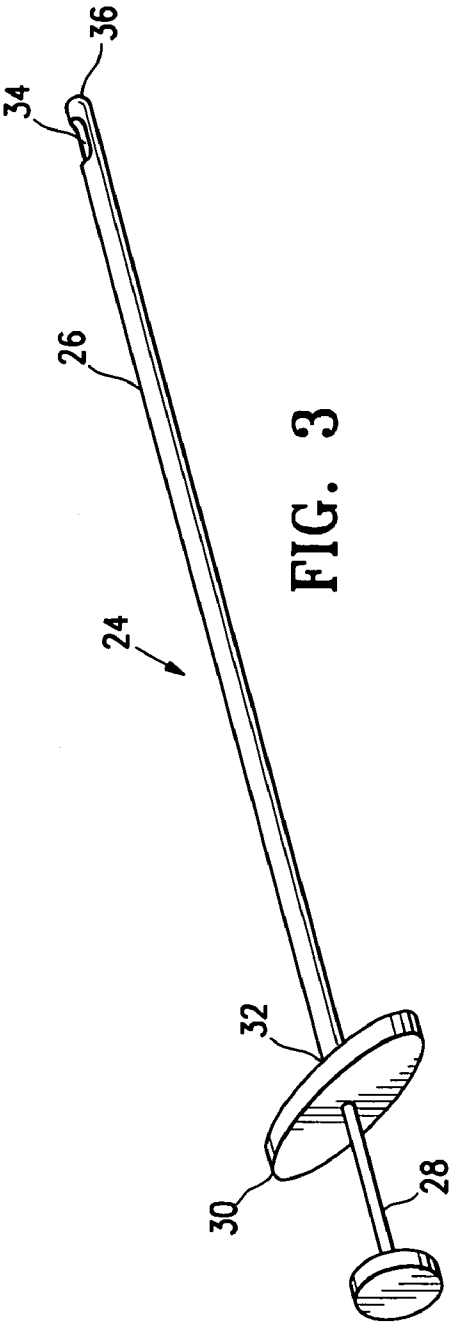


FIG. 3

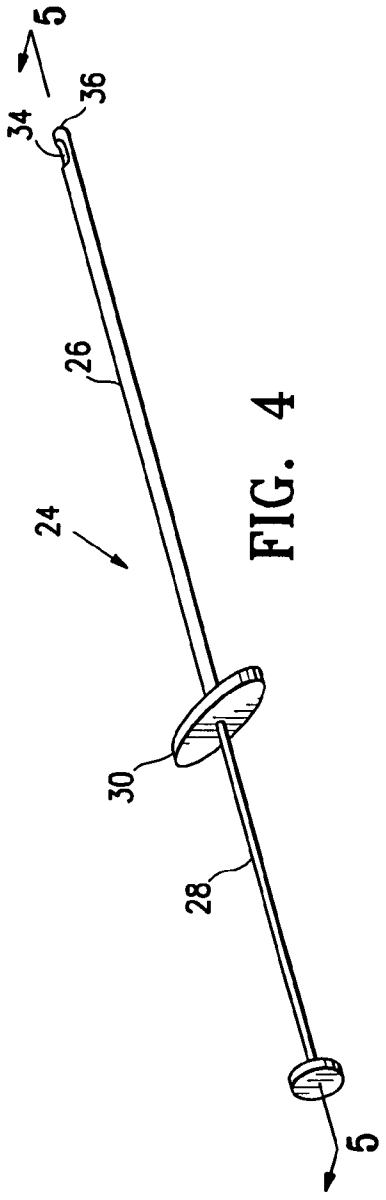


FIG. 4

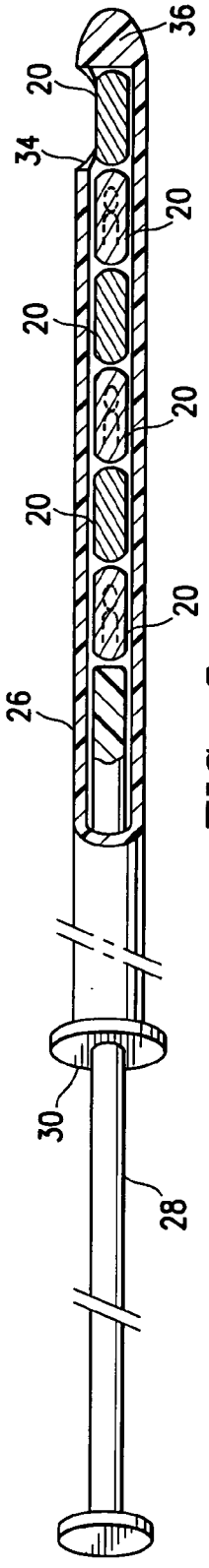


FIG. 5

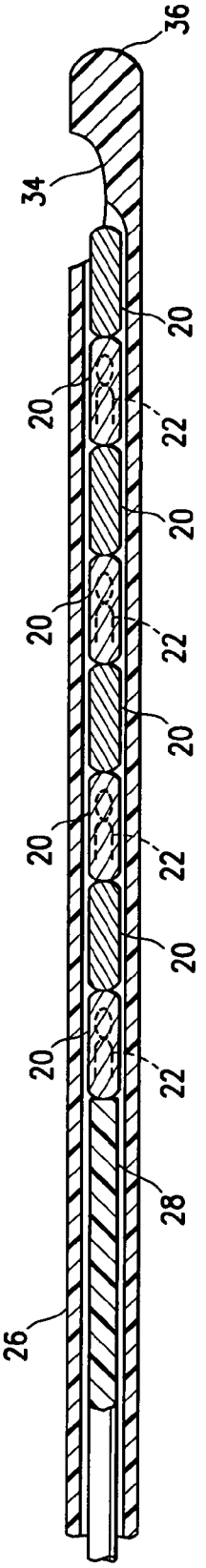


FIG. 6

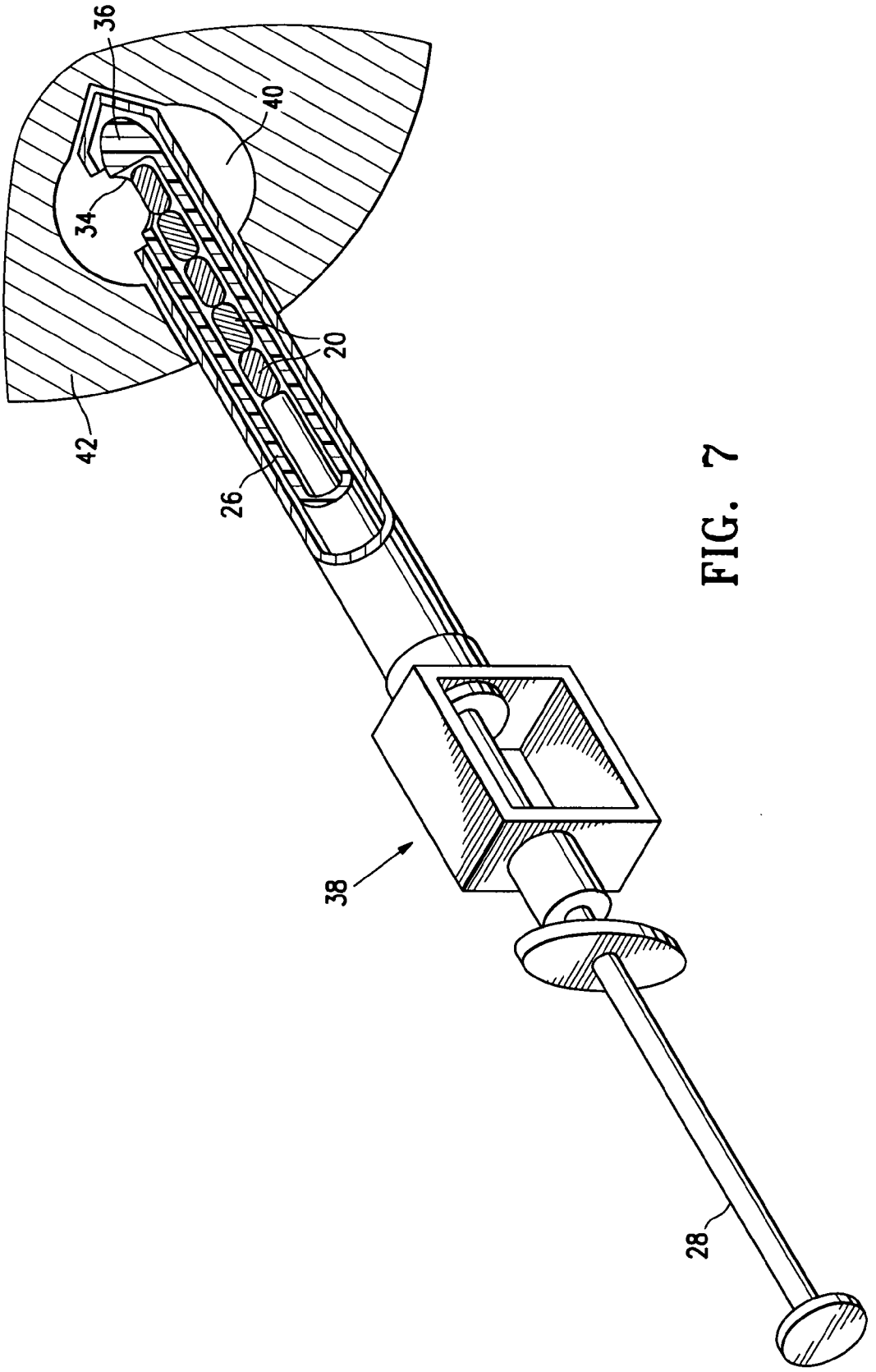


FIG. 7

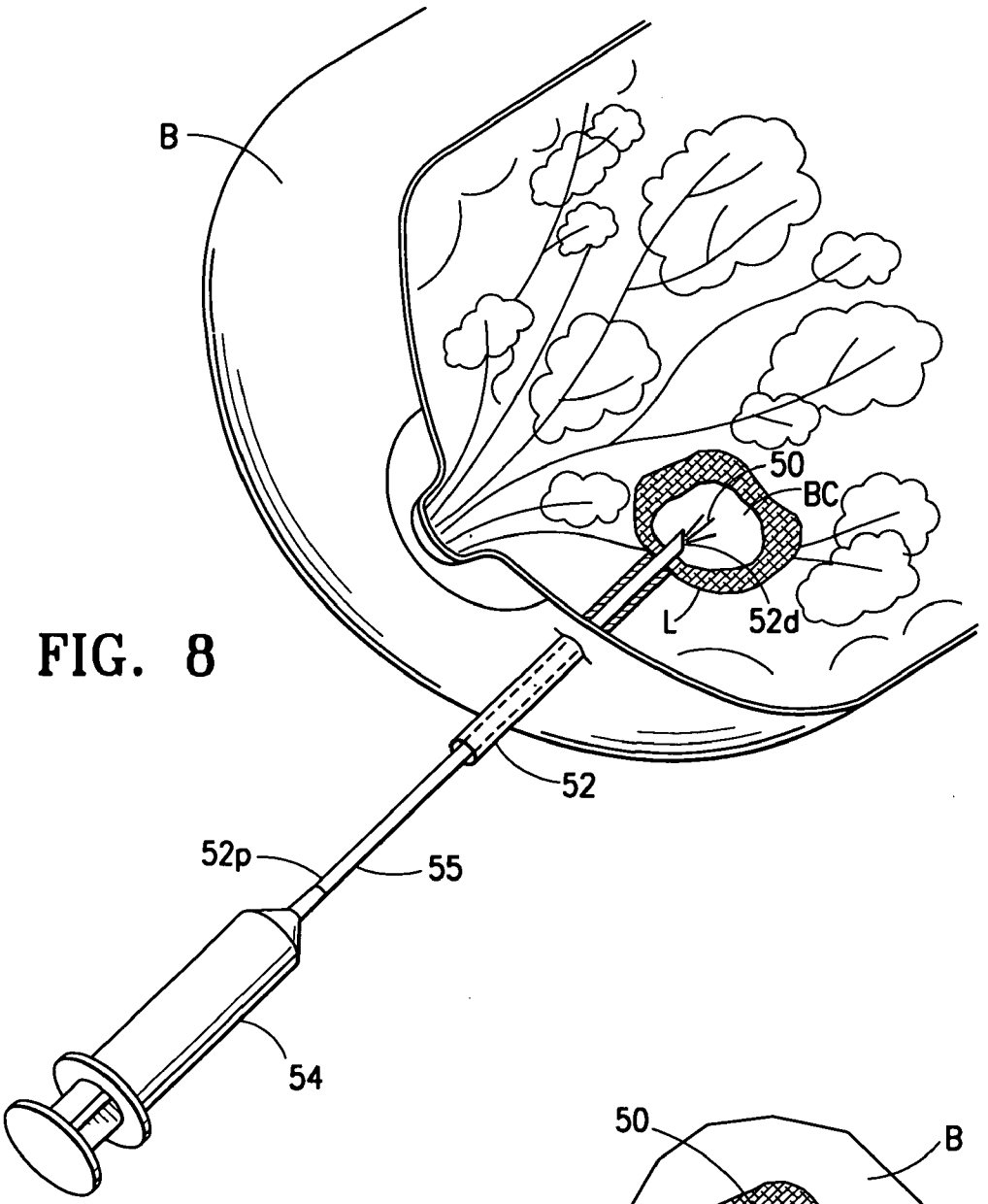


FIG. 8

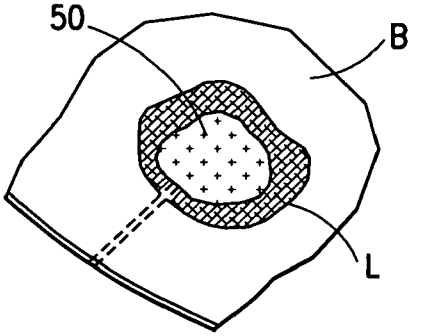


FIG. 8a

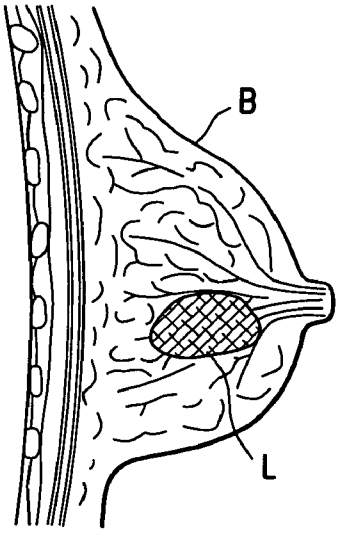


FIG. 9a

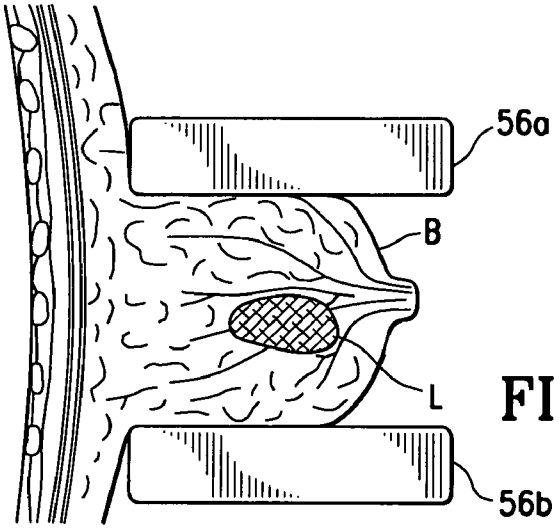


FIG. 9b

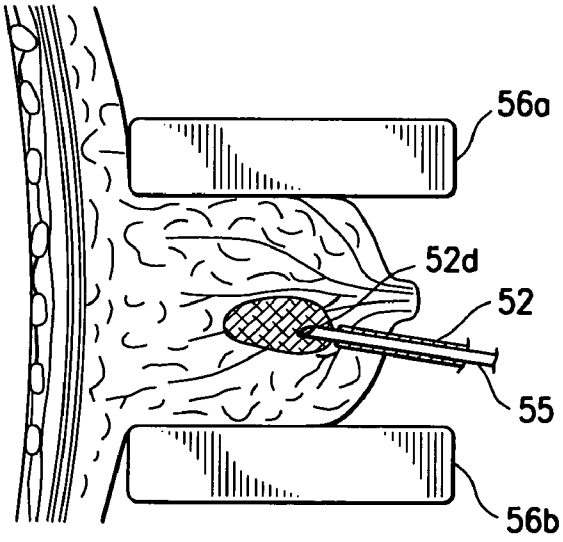


FIG. 9c

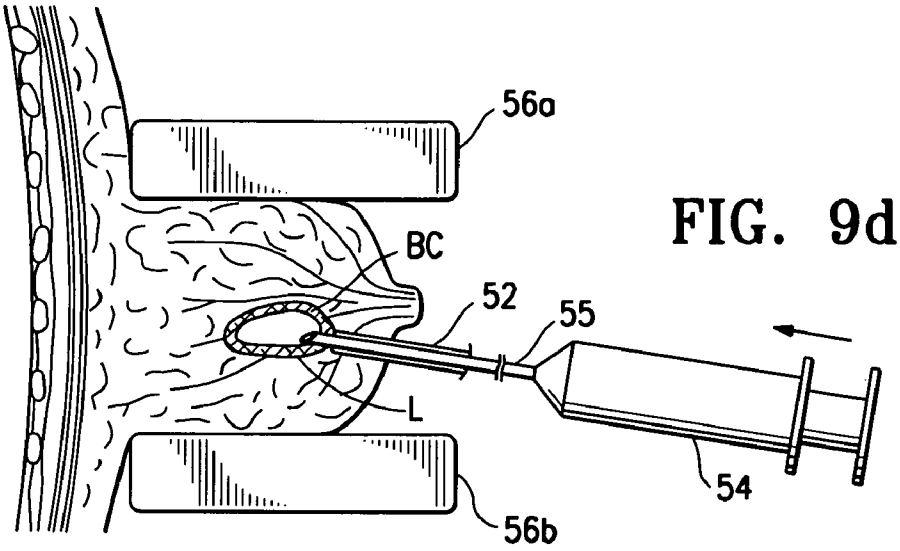


FIG. 9d

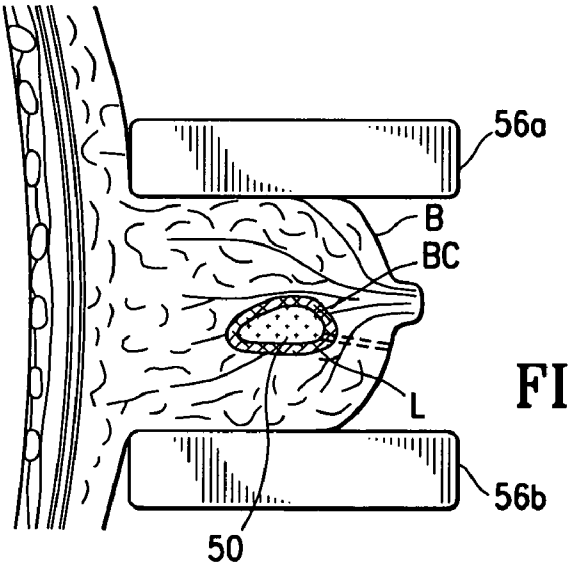


FIG. 9e

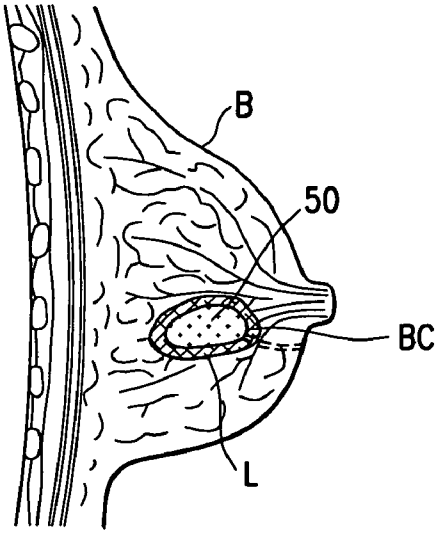


FIG. 9f

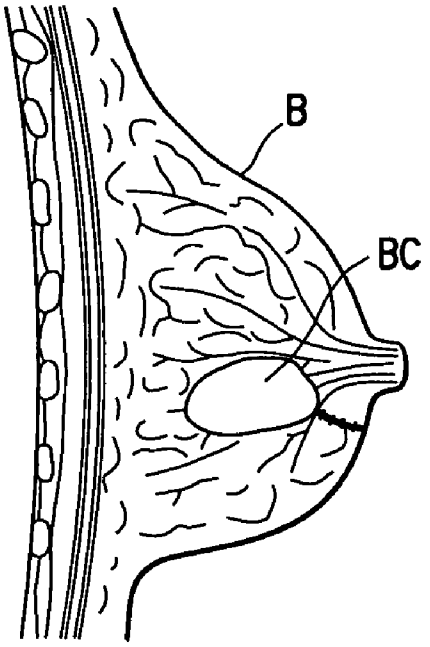


FIG. 9g

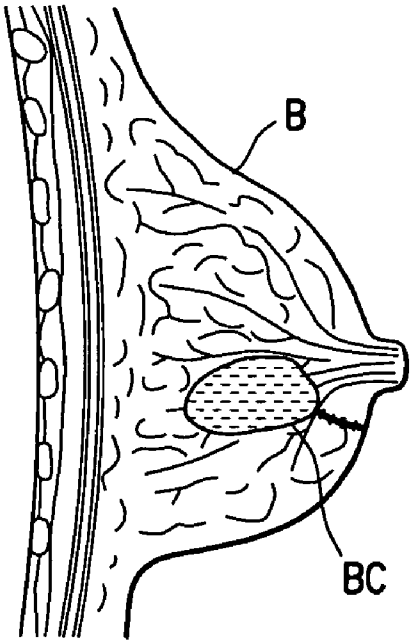


FIG. 9g'

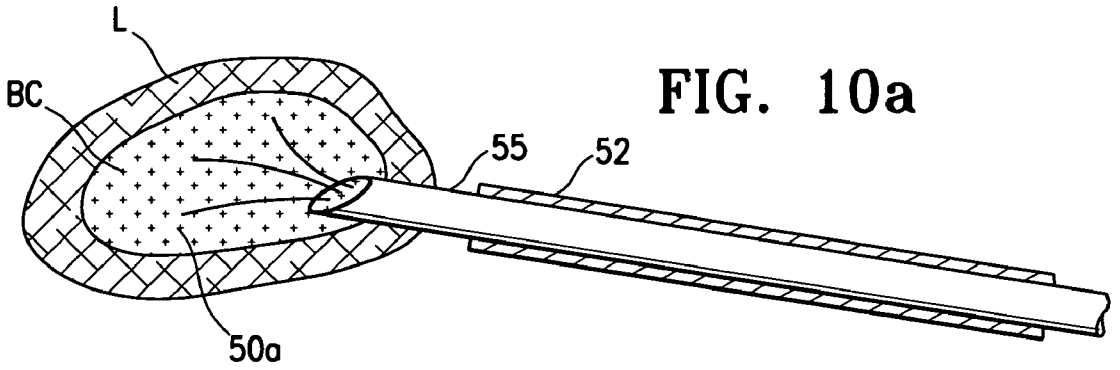


FIG. 10a

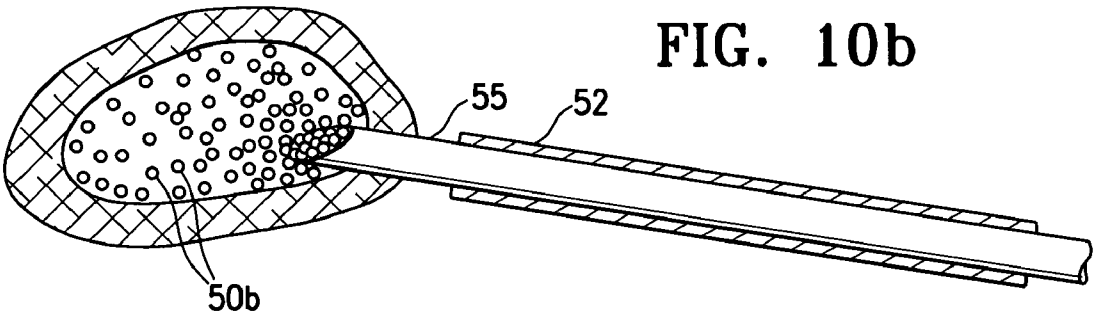


FIG. 10b

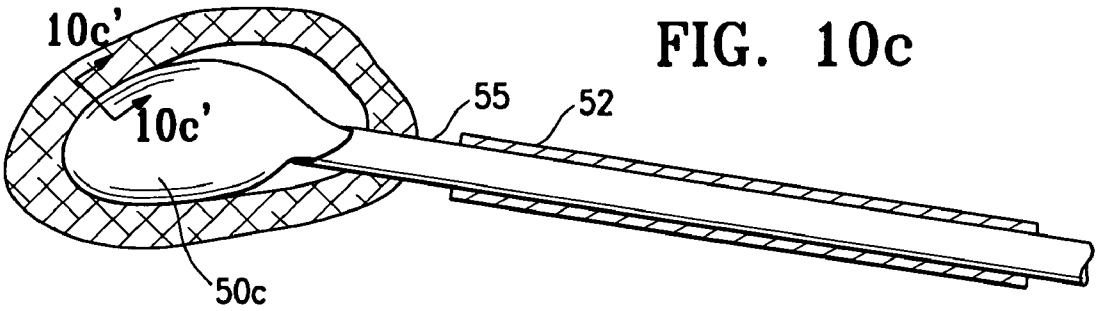


FIG. 10c

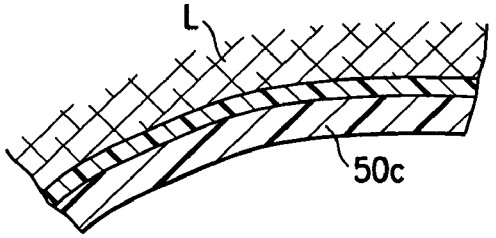


FIG. 10c'

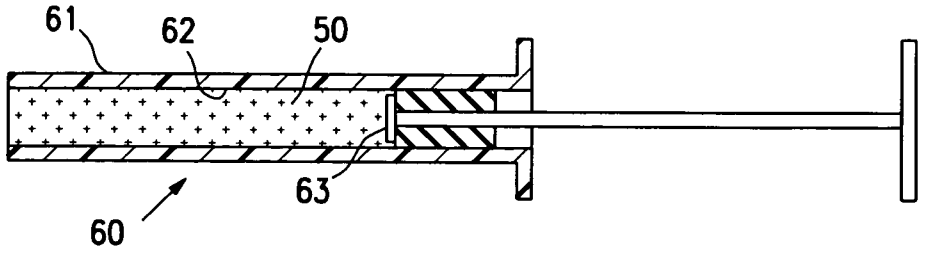


FIG. 11

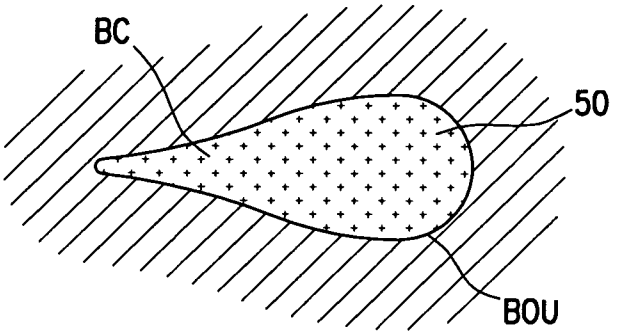


FIG. 12a

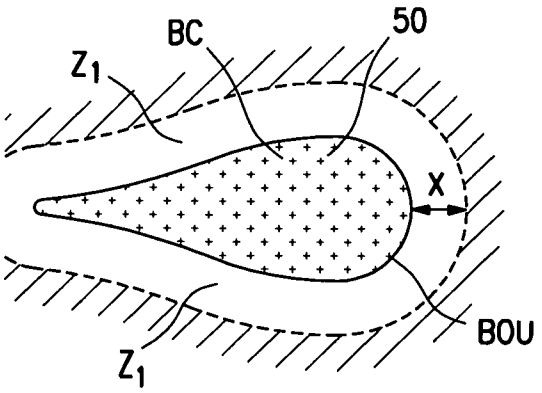


FIG. 12b

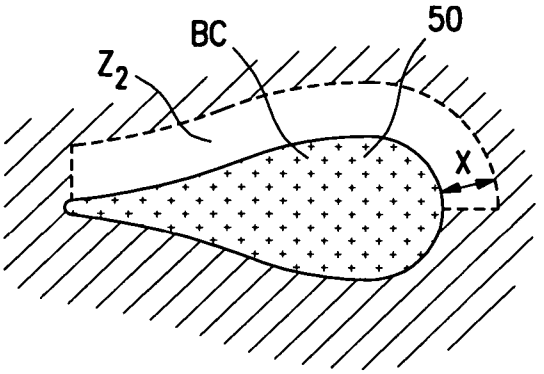


FIG. 12c

IMAGEABLE BIOPSY SITE MARKER

RELATED APPLICATIONS

[0001] This application is a continuation of application Ser. No. 11/258,324, filed Oct. 25, 2005, which is a continuation of application Ser. No. 10/719,448, filed on Nov. 21, 2003, now U.S. Pat. No. 6,996,433, which is a continuation of application Ser. No. 10/684,124, filed on Oct. 10, 2003, which is a continuation of application Ser. No. 10/001,043, filed on Oct. 31, 2001, now U.S. Pat. No. 6,347,241, which is a continuation of application Ser. No. 09/343,975, now U.S. Pat. No. 6,662,041, filed on Jun. 30, 1999, and is a continuation-in-part application to application Ser. No. 09/241,936, filed on Feb. 2, 1999, now U.S. Pat. No. 6,161,034, from which all priority is claimed and which all are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

[0002] The present invention is in the field of markers to be employed at biopsy sites to permanently mark the site, and to methods and apparatus for applying the permanent marker. More particularly, the present invention relates to a marker that is optimally adapted for marking biopsy sites in human breast tissue with permanently placed markers that are detectable by X-ray.

BACKGROUND OF THE INVENTION

[0003] In modern medical practice small tissue samples, known as biopsy specimens, are often removed from tumors, lesions, organs, muscles and other tissues of the body. The removal of tissue samples may be accomplished by open surgical technique, or through the use of a specialized biopsy instruments such as a biopsy needle. A well known state-of-the-art instrument that is often used in connection with the practice of the present invention is known as the "vacuum assisted large core biopsy device".

[0004] After a tissue sample has been removed, it is typically subjected to diagnostic tests or examinations to determine cytology, histology, presence or absence of chemical substances that act as indicators for disease states, or the presence of bacteria or other microbes. The above mentioned and other diagnostic tests and examinations per se are well known in the art and need not be described here. It is sufficient to note that the information obtained from these diagnostic tests and/or examinations is often of vital importance for the well-being of the patient and is used to make or confirm diagnoses and often to formulate treatment plans for the patient. As is known, obtaining a tissue sample by biopsy and the subsequent examination are frequently, almost invariably, employed in the diagnosis of cancers and other malignant tumors, or to confirm that a suspected lesion or tumor is not malignant, and are frequently used to devise a plan for the appropriate surgical procedure or other course of treatment.

[0005] Examination of tissue samples taken by biopsy, often by the above-mentioned "vacuum assisted large core biopsy sampler" is of particular significance in the diagnosis and treatment of breast cancer which is the most common cancer suffered by women in the U.S.A and elsewhere in the industrially developed world. Proper diagnostic procedures, frequent examination by well known techniques such as "mammography" and prompt subsequent surgical treatment have, however, significantly reduced the mortality rate caused by this form of cancer. For this reason, in the ensuing discussion of the pertinent background art and in the ensuing description the invention will be described as used for marking biopsy sites in human and other mammalian breast, although the invention is suitable for marking biopsy sites in other parts of the human and other mammalian body as well.

[0006] Thus, as is known, when an abnormal mass in the breast is found by physical examination or mammography a biopsy procedure follows almost invariably. The nature of the biopsy procedure depends on several factors. Generally speaking, if a solid mass or lesion in the breast is large enough to be palpable (i.e., felt by probing with the fingertips) then a tissue specimen can be removed from the mass by a variety of techniques, including but not limited to open surgical biopsy or a technique known as Fine Needle Aspiration Biopsy (FNAB). In open surgical biopsy, an incision is made and a quantity of tissue is removed from the mass for subsequent histopathological examination. In the FNAB procedure, a small sample of cells is aspirated from the mass through a needle and the aspirated cells are then subjected to cytological examination.

[0007] If a solid mass of the breast is small and non-palpable (e.g., the type typically discovered through mammography), a relatively new biopsy procedure known as "stereotactic needle biopsy" may be used. In performing a stereotactic needle biopsy of a breast, the patient lies on a special biopsy table with her breast compressed between the plates of a mammography apparatus and two separate digital x-rays are taken from two slightly different points of view. A computer calculates the exact position of the lesion with X and Y coordinates as well as depth of the lesion within the breast. Thereafter, a mechanical stereotactic apparatus is programmed with the coordinates and depth information calculated by the computer, and such apparatus is used to precisely advance the biopsy needle into the small lesion. Usually at least five separate biopsy specimens are obtained from locations around the small lesion as well as one from the center of the lesion.

[0008] After the biopsy sample is taken, it may take several days or even a week before the results of the examination of the sample are obtained, and still longer before an appropriate treatment decision is reached. If the decision involves surgery it is clearly important for the surgeon to find the location in the breast from where the tumor tissue has been taken in the biopsy procedure, so that the entire tumor and possibly surrounding healthy tissue can be removed. For example, the particular treatment plan for a given patient may require the surgeon to remove the tumor tissue and 1 centimeter of the tissue surrounding the tumor. A co-pending application for United States Letters Patent by the same inventors discloses markers which are particularly well adapted for marking biopsy sites in the human breast, and which markers remain detectable by X-ray, ultrasound or some other detection technique only for a given time period (i.e. for 6 months) and slowly disappear thereafter, for example by absorption into the body. The purpose of such markers is to facilitate the surgical procedure that is performed while the marker is still detectable. The disappearance of the marker after a longer period of time may be advantageous to avoid obscuring or interfering with follow-up studies or further mammography or other imaging studies.

[0009] In connection with the background art the following specific printed art is mentioned. U.S. Pat. Nos. 2,192,270 and 5,147,307 describe visually discernible markers that are applied externally to the patient's skin. Radiographically

(X-ray) detectable tissue markers (e.g., clips or staples) that are attached to tissue adjacent to the site from which the biopsy specimen has been removed, are described in International Patent Publication No. WO 98/06346. Radiographically visible markers (e.g. marker wires) that may be introduced into the biopsy site and are inserted through the biopsy needle after a tissue sample is removed and which are thereafter allowed to remain protruding from the patient's body, are also described in WO 98/06346. However, due to the consistency of breast tissue and the fact that these biopsy site markers are typically introduced while the breast is still compressed between the mammography plates, these biopsy markers of the prior art may become attached to adjacent bands of connective tissue that do not remain at the specific location of the biopsy after the breast has been decompressed and removed from the mammography apparatus, and may suffer from additional disadvantages as well.

[0010] Thus, there is still a need in the art for of biopsy site markers that are deliverable into the cavity created by removal of the biopsy specimen and not into tissue that is located outside of that biopsy cavity, and which will not migrate from the biopsy cavity even when the breast tissue is moved, manipulated or decompressed. Moreover, such desired markers should remain detectable at the biopsy site i.e. within the biopsy cavity for an indefinite time period, and still should not interfere with imaging of the biopsy site and adjacent tissues at a later point of time, and most importantly should be readily distinguishable in the various imaging procedures from lines of calcifications which frequently are signs for a developing malignancy. The present invention provides such permanent biopsy site markers as well as apparatus and method for delivering such markers into the biopsy cavity.

SUMMARY OF THE INVENTION

[0011] It is an object of the present invention to provide a biopsy site marker that is deliverable into the cavity created by removal of the biopsy specimen.

[0012] It is another object of the present invention to provide a biopsy site marker that does not migrate from the biopsy cavity even when the surrounding tissue is moved, manipulated or decompressed.

[0013] It is still another object of the present invention to provide a biopsy site marker that meets the foregoing requirements and that remains detectable at the biopsy site for an indefinite period of time.

[0014] It is yet another object of the present invention to provide a biopsy site marker that meets the foregoing requirements and that is readily distinguishable by X-ray from granules or lines of calcifications which frequently are signs for a developing malignancy.

[0015] It is a further object of the present invention to provide an apparatus and method for placing into the biopsy cavity a biopsy site marker that meets the foregoing requirements.

[0016] These and other objects and advantages are attained by a biopsy site marker that comprises small bodies or pellets of gelatin which enclose substantially in their interior a radio (X-ray) opaque object. The gelatin pellets are deposited into the biopsy site, typically a cylindrical opening in the tissue created by the recent use of a vacuum assisted large core biopsy device, by injection from an applicator through a tube that is placed into the biopsy site. Typically, several gelatin pellets, only some of which typically do, but all of which may contain the radio opaque object, are deposited sequentially from the applicator into the site through the tube. The radio opaque objects contained in the gelatin bodies have a non-biological shape or configuration to be identifiable as a man-made object such that in observation by typical mammography equipment, that is when viewed from at least two different viewing angles, they do not assume the shape of a line, whereby they are readily distinguishable from granules or lines of calcification.

[0017] The present invention also provides chemical preparations and methods for marking biopsy sites, whereby a detectable marker (i.e., a substance or article that is detectable by imaging and/or palpation and/or visualization) is introduced into the cavity created by removal of a biopsy specimen (e.g., the "biopsy cavity") such that (i) the marker will remain present and detectable at the biopsy at a first time point (e.g. 2 weeks after introduction), and (ii) the marker will clear sufficiently from the biopsy site, or will otherwise be undetectable by imaging so as not to interfere with follow-up imaging of the biopsy site and adjacent tissues at a second time point (e.g. typically 5-8 months and preferably at about 6 months after introduction).

[0018] A. Types of Markers

[0019] (i) Imagable Embodiments of the Marker

[0020] In embodiments of the invention wherein the marker is detectable by imaging, it will typically be imagable by a suitable imaging means or apparatus. For example, the marker may be radiographically visible (e.g., more radiopaque or more radiolucent than the surrounding tissue so as to be imagable by x-ray, CT scan, mammography, fluoroscopy, or other roentgenological means. In other imagable embodiments, the marker may be imagable by other means such as magnetic resonance imaging (MRI), ultrasound, Doppler, or other presently known or hereafter invented imaging techniques.

[0021] (ii) Palpable Embodiments of the Marker

[0022] In embodiments of the invention wherein the marker is detectable by palpation, the marker will comprise a space occupying substance or object(s) that, when introduced into the cavity created by the removal of the biopsy specimen, will form a palpable mass that can be located by closed palpation of the breast and/or by local palpation by a surgeon during dissection of the surrounding breast tissue. Space occupying markers that are palpable include balloon(s), beads, microspheres, of flowable bulking materials such as collagen.

[0023] (iii) Visually Discernible Embodiments of the Marker

[0024] In embodiments of the invention wherein the marker is visually detectable, the marker will comprise a substance or object(s) that is of a color that is different from the color of breast tissue and blood such that, when introduced into the cavity created by the removal of the biopsy specimen, the marker will be visually detectable by a surgeon during dissection of the surrounding breast tissue.

[0025] (iv) Energy-Emitting Embodiments of the Marker

[0026] In some embodiments of the invention, the marker may emit energy that is detectable by a suitable detection apparatus. For example, the marker may comprise a radioactive substance that is detectable by way of a gamma detector, scintillation counter or other apparatus for detecting radiation. Similarly, the marker may comprise a signal emitting apparatus (e.g. a transmitter or transponder) that will continuously, or occasionally when interrogated by ultrasound or other type of interrogating energy, emit a signal (e.g., radiof-

requency, ultrasound, etc.) that can be detected by an apparatus that is useable to detect that particular type of signal.

[0027] (v) Marker Embodiments that are Detectable by More than One Detection Means

[0028] In some embodiments of the invention, the detectable marker may be detectable by a combination of any two or more of the above-summarized imaging, visual, palpation and/or emission/detection techniques. For example, an imagable marker of the present invention may additionally comprise a palpable component as described above (e.g., a space occupying material or article) so as to render the marker both imagable and palpable after implantation at the biopsy site. Alternatively, an imagable marker of the present invention may additionally be provided with a visible component as described above (e.g., a colored substance or article) so as to render the marker both imagable and visually discernible after implantation at the biopsy site. Similarly, by way of illustrative example, an imagable marker of the present invention may additionally comprise a palpable component as described above (e.g., a space occupying material or article) and a visible component as described above (e.g., a colored substance or article) so as to render the marker imagable, palpable and visible during surgery.

[0029] B. Consistency and Properties of the Marker

[0030] (i) Substantially Insoluble Marker Substances

[0031] In accordance with the invention, the detectable marker may comprise a substance (e.g., a gas, lipid, oil, powder, suspension or slurry) that may be delivered into the cavity formed by removal of a biopsy sample (i.e., the "biopsy cavity"), and which has solubility and/or biodistributive properties that allow it to remain present and detectable (e.g., imagable, palpable, energy-emitting and/or visible) at the biopsy site until at least the first predetermined time point (e.g., at least 2 weeks after introduction), but which will allow the substance to be substantially cleared (e.g., dissolved, distributed from or locally metabolized) from the biopsy site at the second predetermined time point (e.g., 6 weeks after introduction).

[0032] (ii) Soluble Marker Substances with Clearance Delaying Element(s)

[0033] Further in accordance with the invention, the detectable marker may comprise a) a detectable (e.g., imagable, palpable, energy-emitting and/or visible) substance that, if delivered alone into the cavity formed by removal of the biopsy specimen, would clear from such biopsy cavity so as to be no longer detectable at the first predetermined time point (e.g., two (2) weeks after introduction) in combination with b) a clearance limiting element (e.g., a diffusion-limiting polymer matrix, a membrane or liposomal encapsulation, a biodegradable matrix or encapsulant, etc . . .) that will limit the dissolution, biodistribution and/or local metabolism of the detectable substance to remain present and detectable at the biopsy site for at least 2 weeks after introduction, but which will allow the detectable substance to be substantially cleared (e.g., dissolved, distributed from or locally metabolized) from the biopsy site at the second predetermined time point (e.g., 5-8 months and preferably at about 6 months after introduction).

[0034] (iii) Markers that do No Interfere with Subsequent Imaging Studies

[0035] Still further in accordance with the invention, the detectable marker may comprise a substance or article that is detectable by a detection method that is different from the imaging method that is intended to be used for follow-up imaging of the biopsy site and adjacent tissues, thus allowing the marker to reside at the biopsy site beyond the second time point (i.e., that time point at which follow-up imaging studies are to be conducted) or even indefinitely, without interfering with such follow-up imaging studies. For example, the marker may be detectable by palpation, visualization and/or ultrasound but not visible on x-ray, thereby allowing for follow-up x-ray studies without interference by the marker while remaining locatable by palpation, visualization, specialized detection and/or ultrasound in the event that a surgeon, radiologist or other practitioner may wish to subsequently locate the biopsy site.

[0036] (iv) Markers that Adhere to the Wall(s) of the Biopsy Cavity

[0037] Still further in accordance with the invention, the detectable marker of the present invention may comprise, or may be combined with, an adhesive which will cause the detectable marker to adhere to tissue immediately adjacent the void created by removal of the biopsy sample.

[0038] C. Methods for Using Biopsy Site Markers of the Present Invention

[0039] Still further in accordance with the invention, there are provided methods for surgical excision of tissue that is located adjacent to or surrounding a biopsy cavity in which a visually detectable marker of the present invention has been delivered. The method generally comprises the steps of a) visualizing the perimeter of the visually discernible marker and b) excising tissue that lies adjacent to the perimeter of said visually discernible marker. This method of surgical excision may be used to accurately excise and remove a quantity of tissue of a specific width (e.g., a region or band that is 2 centimeters wide) that surrounds or lies adjacent to the original biopsy cavity. Because the biopsy site markers of the present invention actually occupy the original biopsy cavity, they serve to accurately mark the perimeter of that biopsy cavity. As such, the surgeon is able to accurately visualize the boundary of the biopsy cavity and to then excise and remove tissue that lies within a certain distance (e.g., 2 centimeters) of that cavity boundary. Such visualization of the biopsy cavity boundary may be made easier or enhanced when the biopsy site marker comprises, in addition to a visually discernible component such as a dye or carbon particles, a space-occupying bulking agent as described above in reference to palpable embodiments of the invention as the presence of such space occupying or bulking agent may serve to dilate or distend the biopsy cavity, thereby making it easier for the surgeon to visualize the boundaries of that biopsy cavity. This surgical excision method may be particularly suitable in cases where the histopathological evaluation of the biopsy specimen suggests that additional cancerous cells may continue to reside in tissue located within a certain distance of the original biopsy cavity boundary.

[0040] The features of the present invention can be best understood together with further objects and advantages by reference to the following description, taken in connection with the accompanying drawings, wherein like numerals indicate like parts.

[0041] Additional objects, embodiments and advantages of the present invention will become apparent to those of skill in the relevant art upon reading and understanding of the following detailed description of preferred embodiments and the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0042] FIG. **1** is a perspective view of a preferred embodiment of the biopsy site marker of the present invention.

[0043] FIG. **2** is a perspective view of a plurality of biopsy site markers in accordance with the first embodiment of the present invention.

[0044] FIG. **3** is a perspective view of an applicator apparatus in accordance with the present invention, for depositing the biopsy site marker at a biopsy site.

[0045] FIG. **4** is a perspective view of the applicator apparatus of FIG. **3**, showing the applicator with an extended piston indicating that the applicator is loaded with biopsy site markers.

[0046] FIG. **5** is a cross-sectional view of the site marker shown in FIG. **4**, the cross section taken on lines **5-5** of FIG. **4**.

[0047] FIG. **6** is an enlarged cross sectional view showing the applicator of FIG. **4** loaded with biopsy site markers in accordance with the present invention.

[0048] FIG. **7** is a schematic view of a human breast, showing a biopsy cavity of the type obtained by a vacuum assisted large core biopsy sampler, into which a plurality of biopsy markers are deposited in accordance with the present invention.

[0049] FIG. **8** is a perspective view of a human breast having a lesion from which a biopsy specimen has been removed, and showing a syringe and introduction cannula operatively positioned for introduction of a detectable marker of the present invention into the cavity created by removal of the biopsy specimen.

[0050] FIG. **8***a* is an enlarged perspective view of a portion of the breast of FIG. **8** after the detectable marker has been introduced and after the syringe and introduction cannulas have been removed.

[0051] FIGS. **9***a*-**9***g* are schematic, step-by-step showings of a preferred method for using a detectable marker of the present invention to mark the site of a lesion that has been biopsied while the breast is compressed within a mammography apparatus.

[0052] FIG. **10***a* is a schematic showing of a first embodiment of a detectable marker of the present invention after introduction into a biopsy site.

[0053] FIG. **10***b* is a schematic showing of a second embodiment of a detectable marker of the present invention after introduction into a biopsy site.

[0054] FIG. **10***c* is a schematic showing of a third embodiment of a detectable marker of the present invention after introduction into a biopsy site.

[0055] FIG. **11** is a longitudinal sectional view of an injector device that is useable to introduce a solid (e.g., powdered, particulate or granular) marker substance of the present invention into a biopsy site.

[0056] FIGS. **12***a*-**12***c* are showings of a preferred method of excising and removing tissue that lies within a predetermined zone located on all sides or only one side of the boundary of a previously-created biopsy cavity.

DETAILED DESCRIPTION OF EMBODIMENTS OF THE INVENTION

[0057] The following specification taken in conjunction with the drawings sets forth the preferred embodiments of the present invention. The embodiments of the invention disclosed herein are the best modes contemplated by the inventors for carrying out their invention in a commercial environment, although it should be understood that various modifications can be accomplished within the parameters of the present invention.

[0058] Referring now to the drawing figures and particularly to FIGS. **1** and **2**, a body **20** of gelatin or reconstituted collagen in the shape of a pellet that includes or incorporates a radio-opaque marker **22** of a definite shape is disclosed. The gelatin or reconstituted collagen body **20** can be of virtually any shape or configuration, however the herein shown shape of a cylinder or pellet is preferred. The gelatin body of pellet **20** is of such size that several of the pellets can be deposited in a biopsy site, such as a typical biopsy site obtained by using the vacuum assisted large core biopsy device that is frequently used in current medical practice. The gelatin body or pellet **20** is stored and is applied, that is deposited in the biopsy site, in a dehydrated form through an applicator device that forms another aspect of this invention. However, when the gelatin body or pellet **20** of the invention is not deposited through the applicator device, it does not necessarily need to be stored and applied in a dehydrated form. Nevertheless, storing the gelatin pellets **20** in dehydrated form increases their useful shelf-life and renders it easier to keep them sterile.

[0059] After having been deposited at the biopsy site the gelatin marker **20** slowly absorbs moisture from the surrounding tissue and becomes hydrated. In the dehydrated form, shown in the appended drawing figures, the gelatin body or pellet **20** is approximately 1 to 3 mm in diameter and is approximately 5 to 10 mm long. The presently preferred embodiment of the gelatin pellet **20** is approximately 2 mm in diameter and is approximately 8 mm long. After the pellet **20** has reached hydration equilibrium with the surrounding tissue it becomes approximately 3 to 5 mm in diameter and approximately 10 to 15 mm long. After hydration the presently preferred embodiment of the pellet **20** is approximately 4 mm in diameter and approximately 10 mm long.

[0060] The gelatin or reconstituted collagen material itself is observed under ultrasound examination as a white spot because of the air pockets usually entrapped in its matrix. In mammography the gelatin is observed as dark spots in normal breast, because of the presence of the air pockets. In a fatty breast viewed by mammography the gelatin marker is observed as a lighter area containing dark spots, due to the water in the hydrated gelatin absorbing more energy than the surrounding matrix and the air pockets within the matrix. A pellet **20** or plurality of pellets **20** due to their bulk may also be palpable and locatable by tactile means within the breast tissue or other tissue. The gelatin or reconstituted collagen marker itself can be made even more radio-opaque by ion-impregnation and chelation techniques which are described in detail in the aforesaid co-pending application Ser. No. 09/241,936 filed on Feb. 2, 1999 by the same inventors in connection with the description of biopsy markers of that application, and the description of this method of rendering the gelatin markers radio-opaque is also provided here below. The disclosure of co-pending application Ser. No. 09/241,936 is incorporated herein by reference in its entirety. The gelatin or reconstituted collagen material can also be made more radio-translucent by entrapping (mixing) a substantial amount of air in the gelatin. Moreover, a visually detectable substance, such as carbon particles, or a suitable dye (e.g. methylene blue or indigo) may also be added to the gelatin to make the marker visible by a surgeon during dissection of the surrounding breast tissue.

[0061] The gelatin or reconstituted collagen per se does not serve as a permanent marker of the biopsy site because it is eventually reabsorbed by the body, although the dye or even

ionic material that made the gelatin visible or radio-opaque, respectively, may remain at the site for longer time period than the palpable gelatin pellet, and may remain there indefinitely. Factors which influence how long the gelatin or reconstituted collagen pellet remains at the site, and various means to adjust this time period are described in the aforementioned co-pending application Ser. No. 09/241,936.

[0062] It is a novel and important aspect of the present invention to incorporate into the gelatin or reconstituted collagen body or pellet **20** the radio-opaque marker **22**. The radio-opaque or X-ray detectable marker **22** that is incorporated or enclosed in the gelatin pellet **20** must have the following properties. First, by its very nature it must be detectable by X-ray, including the type of radiography used in the practice of mammography. It must be comprised of a material or composition that is not absorbed by the body and stays for indefinite time at the biopsy site, retains its shape and remains X-ray detectable at the biopsy site also for an indefinite time. The material or composition of the radio-opaque marker **22** must, of course, be biocompatible at the site where it is deposited. Another important requirement is that the biocompatible marker must have an identifiable specific non-biological shape or form. The purpose of specific form for the marker is to render the marker distinguishable under X-ray or in a mammographic examination from naturally formed calcification granules or a line of such granules, which are also X-ray opaque. As is known, a line of calcification which normally forms along ducts is considered a sign of developing malignancy. Thus, the marker **22** should be of such specific configuration that when it is viewed sterically, as during a mammography examination, it should be distinguishable from an X-ray opaque line. Numerous specific shapes or configurations satisfy the foregoing requirements, however amorphous X-ray opaque material that would be uniformly (or substantially uniformly) distributed in the gelatin pellet **20** is unlikely to satisfy these requirements.

[0063] Materials or compositions which are suitable for the marker **22** include metal, such as stainless steel, tantalum, titanium, gold, platinum, palladium, various alloys that are normally used in bioprosthesis and ceramics and metal oxides that can be compressed into specific shapes or configurations. Among these the use of biocompatible metals is presently preferred, and the herein described preferred embodiment of the marker **22** is made of stainless steel. Generally speaking the marker **22** is approximately 0.01 to 0.06 inches wide, approximately 0.03 to 0.2 inch long and approximately 0.002 to 0.02 inch thick. The presently preferred permanent marker **22** shown in the drawing figures has the configuration or shape approximating an upside down turned Greek letter gamma, is approximately 0.10 inch long and approximately 0.04 inch wide. The upside-down Greek letter gamma shape is believed to be unique, has some resemblance to the popular breast cancer awareness ribbon and is readily distinguishable under X-ray and mammography as a "man-made" marker object from any naturally formed X-ray opaque body. Various manufacturing techniques which per se are well known in the art, can be utilized to manufacture the X-ray opaque permanent marker **22**. Thus, the marker **22** can be formed from wire, or can be electrochemically etched or laser cut from metal plates. The presently preferred embodiment of the gamma shaped marker **22** is formed by electrochemical etching from stainless steel plates.

[0064] FIGS. **1**, **2** and the other drawing figures, as applicable, show only one marker in the gelatin pellet **20**, although more than marker may be incorporated in the pellet **20**. FIG. **1** discloses a cylindrically shaped gelatin pellet **20** that in accordance with the present invention includes the gamma shaped stainless marker **22**, and as an optional feature also includes a dye or other coloring material (e.g. indigo) that also stays substantially permanently at the biopsy site and is visible by a surgeon when the breast tissue is dissected, as in an operation where tumor tissue is removed (lumpectomy). Gelatin bodies or pellets **20** all of which include one or more permanent radio opaque markers **22** in accordance with the present invention may be deposited at a biopsy site. Alternatively, a series of gelatin bodies or pellets **20** where only some but not all include a permanent X-ray opaque marker **22** of unique non-biological shape, may be deposited at the biopsy site. Preferably, a series of pellets **20** are deposited where each second, each third, or each fourth etc., pellet includes the marker **22**. FIG. **2** discloses an example of a series or sequence of pellets **20** where each second pellet **20** includes the metal marker **22** and where each pellet **20** that does not include the metal marker **22** includes carbon black or dye that is visible to the surgeon during operation. In this connection it should be understood and appreciated that as noted above the gelatin bodies or pellets **20** themselves serve a purpose of marking the biopsy site for a predetermined length of time, that is until they become absorbed by the body.

[0065] The drawing figures, particularly FIGS. **1** and **2** show the metal marker **22** disposed substantially in the center of the cylindrical gelatin pellet **20**. This is preferred but is not necessary for the present invention. The metal marker **22** can be embodied in or included in the gelatin body **20** virtually anywhere. The gelatin body or pellet **20** however has to have sufficient integrity or firmness to retain the metal marker **22** and air bubbles which are usually deliberately entrapped in the gelatin. As is known, the firmness or bodily integrity of gelatin is measured in units of Bloom. Generally speaking it was found in accordance with the present invention that the higher the Bloom strength of the gelatin used in the marker **20** the better the marker performs. The higher Bloom strength gelatin holds gas bubbles within its matrix better than lower Bloom strength gelatin. Gelatin with a Bloom strength of approximately 150 especially **175** is adequate for the practice of the present invention, but a more preferred range is 200 to 300 Bloom, the most preferred range being between 250 and 300. (For comparison, typical food gelatin is approximately 75 Bloom, and gelatin of 300 Bloom feels like a soft rubber eraser.)

[0066] A description how to obtain gelatin or reconstituted collagen bodies suitable for use as markers **20** with various properties, before the permanent radio-opaque metal or like marker **22** of specific form is incorporated therein, is provided below in connection with following examples.

[0067] Example of Radiograpically Visible/Palpable Marker Material Formed of Metal Ions in Combination with a Collagenous or Gelatinous Matrix

[0068] U.S. Pat. No. 4,847,049 (Yamamoto incorporated herein by reference) describes an ion-impregnation or chelation technique whereby an ion may be impregnated or chelated to collagen for the purpose of imparting antimicrobial properties to the collagen preparation. Thus, using this technique, imagable ions such as radiographically visible metal ions, may be bound to a bulky collagenous material to form a marker **10** that may be a) imaged by radiographic means and b) located by palpation of tissue surrounding the biopsy site.

For example, a silver ion-renatured collagen composition may be prepared by the following process:

[0069] Step 1—Renaturation of Collagen (or Gelatin)

[0070] Collagen may be renatured to an insoluble form by processing of denatured collagen that has been obtained from a natural source such as bovine corium (hide), bovine tendon, and porcine skin. Alternatively, pre-processed, insoluble collagen may be purchased in the form of a commercially available hemostatic material such as Collastat™ and Avitene™ nonwoven web. Methods for renaturing collagen are known in the literature, including, for example, those methods described in U.S. Pat. Nos. 4,294,241 and 3,823,212. The specifications of U.S. Pat. Nos. 4,294,241 and 3,823,212 are incorporated herein by reference.

[0071] A particularly preferred form of renatured collagen for utilization in accordance with the present invention is one that has been renatured and covalently cross-linked. This collagen may be prepared by utilizing readily available polyfunctional cross linking agents or fixatives, such as dialdehydes, dicarboxylic acids, diamines, and the like. Typically, tropocollagen is dissolved in a buffer of pH 3.0 to 5.0 to provide a solution containing approximately 1 to 2% by weight of the collagen. Then 1% of a dialdehyde cross-linking agent such as glutaraldehyde or formaldehyde is then added. The mixture is then frozen and stored for approximately 24 hours. After thawing and washing to remove unreacted cross linking agent, the renatured cross-linked collagen is then ready for contact with a silver ion-containing solution.

[0072] Step 2—Binding of Metal Ions to the Renatured Collagen

[0073] The source of silver ion may be a water soluble silver salt, preferably silver nitrate. While the concentration of the silver ion in the solution is not particularly critical, it will be usually convenient to utilize solutions in the concentration range of about 10 to 10 millimolar.

[0074] The renatured collagen is preferably contacted with a silver ion-containing solution in the pH range of about 4 to 9. The pH of the silver ion-containing solution can be controlled by the addition of an appropriate titrating agent, such as nitric acid, or potassium hydroxide, as required, to maintain the pH at less than about 9.0 to avoid the degradation of the silver. There is not believed to be any lower limit for the pH, however, normally a pH above 4.0 will be convenient. A particularly preferred range for the pH is from 7.0 to 7.5. The binding capacity of silver by collagen is particularly effective within this preferred pH range, although the amount of binding by silver by the collagen is further controllable by the concentration of the silver ion-containing solution and/or exposure time of the collagen to the silver ion-containing solution. Simultaneous with or subsequent to exposure of the collagen to the silver ion-containing solution, the collagen is then exposed to ultraviolet radiation of energy and duration sufficient to strengthen the binding of the silver ions to the collagen without substantial formation of metallic silver formed as a result of oxidation of various functional groups in the collagen by the silver ion. While the exact limits of the ranges of the conditions which will be sufficient to strengthen the binding of the silver ions without substantial formation of metallic silver are not precisely determinable, it will generally suffice to maintain the pH of the silver-collagen environment at less than 8.0 while exposing the collagen to ultraviolet radiation in the range of about 210 to 310 nm wavelength for about from 5 to 15 minutes. The time of UV exposure for complete reaction is inversely proportional to the light intensity which is preferably in the range of 100 to 1,000 microwatts/cm^2. A slight coloration of the collagen due to the exposure to ultraviolet radiation is acceptable, i.e., a turning from white to a light brown to yellow color, indicating a slight oxidation reaction occurring in the collagen, however, the radiation should not be to the extent that dark brown or black areas in the collagen occur due to over-oxidation and/or substantial formation of metallic silver. Normally the exposure will be performed at ambient temperatures, i.e., in the range of about 20° to 25° C., however, there is not believed to be any reason why the exposure could not occur at higher or lower temperatures providing that the temperature is not high enough to cause degradation of the collagen and/or silver ion. There is not believed to be any lower limit to the temperature at which the exposure may take place, provided it is above the freezing point of the ion-containing solution. Ultraviolet radiation may be provided by any conventional ultraviolet radiation source of appropriate wavelength, such as germicidal lamps and mercury/xenon lamps.

[0075] Step 3 (Optional)—Addition of Visible Component to Marker

[0076] If it is desired for the marker to be detectable visually, as well as by imaging and palpation, a quantity of a visible substance having a color dissimilar blood or tissue may be added. For example, carbon particles or a dye (e.g., methylene blue, indigo) may be added to the above-prepared silver ion/collagen preparation to provide a colored silver ion/collagen marker **10** that is imagable (by radiographic means), palpable (by hand) and visible (under white light in the operating room).

[0077] The above-described collagen-metal ion marker **10** (with or without visible marker component) is introduced into the cavity created by removal of the biopsy specimen. The quantity of this marker **10** introduced may be sufficient to distend or stretch the biopsy cavity somewhat, thereby creating a more palpable and obvious mass of marker material at the biopsy site.

[0078] Renatured gelatin or a cross-linked gelatin preparation such as Gelfoam.™. may be impregnated or combined with a metal ion to provide a gelatin-metal ion marker material. The gelatin may be prepared and ion-bound by the same method as set forth hereabove for collagen.

[0079] Example of Radiographically or Ultrasonically Visible/Palpable Marker Material

[0080] Step 1—Renaturation of Collagen (or Gelatin)

[0081] Collagen or gelatin is renatured, as by the method described in Step 1 of the immediately preceding example and described in the literature, including, for example, those methods described in U.S. Pat. Nos. 4,294,241 and 3,823,212.

[0082] Step 2—Dispersing of Air or Other Gas in the Renatured Collagen or Gelatin Matrix

[0083] Air or another biologically inert gas (e.g., carbon dioxide) is then dispersed throughout the renatured collagen or gelatin matrix by a suitable means such as mixing, mechanical blending, nucleation, bubbling, etc. This results in the formation of many small gas bubbles throughout the collagenous or gelatinous matrix and provides a marker substance that can be introduced into the biopsy cavity through a cannula or tube and is substantially more radio-lucent than the tissue surrounding the biopsy cavity. In this regard, this marker can be imaged by x-ray or ultrasound but will not block or obscure imaging of tissue that lies immediately adjacent the biopsy cavity. Also, because of the bulk of the

collagen or gelatin matrix, the marker is readily palpable and locatable by tactile means within the surrounding breast tissue or other tissue.

[0084] Step 3 (Optional)—Addition of Visible Marker Component

[0085] If it is desired for the marker to be detectable visually, as well as by imaging and palpation, a quantity of a visible substance having a color dissimilar to blood or tissue may be added. For example, carbon particles or a dye (e.g., methylene blue, indigo) may be added to the above-prepared silver ion/collagen preparation to provide a colored silver ion/collagen marker **10** that is imagable (by radiographic means), palpable (by hand) and visible (under white light in the operating room).

[0086] In routine use, the above-described collagen/gas or gelatin/gas marker **10** (with or without visible marker component) is introduced into the cavity created by removal of the biopsy specimen. The quantity of this marker **10** introduced may be sufficient to distend or stretch the biopsy cavity somewhat, thereby creating a more palpable and obvious mass of marker material at the biopsy site.

[0087] Preferred Example of Preparing Cylindrically Shaped Gelatin Pellets **20** Having a Colorant and Including the Permanent Marker

[0088] 80 grams of dry gelatin obtained from porcine skin is mixed into 1000 ml of hot water (180° F.). Variations in gelatin to water ratio will change the consistency but are nevertheless permissible within the scope of the invention. The 80 grams of gelatin is about the maximum amount which will dissolve in water without modifications to pH. The gelatin is then fully dissolved in the water with slight mixing. In a separate container, 1.6 grams of indigo colorant is mixed into 20 ml of ethyl alcohol. Then the ethanol solution of the colorant is added by mixing to gelatin dissolved in water. Air is then whipped into gelatin mixture to froth the mixture.

[0089] The gelatin dissolved in water is then poured into molds (not shown) which have the shape of the desired gelatin body. In the preferred embodiment the mold is shaped to provide the cylindrical pellet shown in the drawing figures. One gamma (.gamma.) shaped permanent marker **22**, made by chemical etching from stainless steel plates, is deposited into the gelatin in each mold. (In alternative embodiments more than one marker **22** may be deposited into each mold.) Due to the viscosity of the gelatin solution the marker **22** does not usually sink to the bottom of the mold. The top of the plate (not shown) holding a plurality of molds is squeegeed to level the mixture.

[0090] After cooling to approximately 40° F. or cooler temperature the gelatin sets and provides the gelatin body **20** that incorporates the permanent marker **22** However, in order to dehydrate the marker it is first frozen and thereafter lyophilized in commercial lyophilization apparatus. Gelatin pellets containing the permanent marker **22** but not having a colorant can be prepared in the same manner, but without adding indigo dye or other colorant. Gelatin bodies or markers **20** that do not include or incorporate a permanent marker **22** can also be made in this manner, but without depositing the marker **22** into the gelatin after it has been placed into the mold. The gelatin body **20** prepared in this manner is reabsorbed from the biopsy site by the human body in approximately three weeks, whereas the permanent marker **22** remains indefinitely.

[0091] Description of the Applicator Apparatus and its Use in Conjunction with the Biopsy Marker of the Invention

[0092] Referring now to FIGS. **3-7** the applicator device or apparatus **24** with which the biopsy markers of the invention are preferably applied or deposited, is disclosed. In this connection it should be understood that the biopsy markers of the invention can be used without the applicator, and can be deposited in accordance with the various methods and techniques utilized in the state-of-the-art. However, a preferred technique of applying the biopsy markers of the invention is to place or deposit them in a biopsy cavity that is obtained with a vacuum assisted large core biopsy device of the type presently used in the state-of-the-art. Such a device, distributed for example by Johnson and Johnson Endo Surgery is well known in the art, and is schematically shown in FIG. **7**.

[0093] The applicator **24** of the invention comprises an elongated cylindrical body **26** having an interior cavity and a piston **28** that fits and slides back and forth in the elongated cylindrical body **26**. The cylindrical body **26** has an enlarged disk **30** at one end **32**. The disk **30** serves to render it convenient for a user (not shown) to operate the applicator **24**, as is described below. The cylindrical body **26** that can also be described as an elongated flexible tube has an opening **34** that commences a relatively short distance, that is approximately 0.3 inch before its other, closed end **36**. The opening **34** is configured to form a ramp in the side of the tube **26**. The outer diameter of the tube **26** is such that it fits through the vacuum assisted large core biopsy device **38** shown in FIG. **7**. In this connection it should of course be understood that the precise dimensions of the tube **26** are coordinated with the dimensions of the piston **28** and with the vacuum assisted large core biopsy device **38**. Moreover, the diameters of the gelatin pellets **20** in their dehydrated form are also coordinated with the inner diameter of the cylinder or tube **26**. The cylinder or tube **26** and the piston **28** can be made from any appropriate medical grade plastic material, and is preferably made of high density polyethylene. The outer diameter of the presently preferred embodiment of the cylinder or tube **26** is approximately 0.093 inch and its inner diameter is approximately 0.07 inch.

[0094] In the preferred manner of using the biopsy markers of the present invention having the permanent markers **22** incorporated in a gelatin body **20**, as well as using biopsy markers that have only the gelatin body **20** without a permanent marker **22**, the applicator device **24**, more precisely the tube **26** is loaded with a desired number of pellets **20**, as is shown in FIGS. **4-6**. Any number of pellets **20** within the range of 1 to approximately 30 may be loaded within the tube **26**, however presently it appears that approximately 8 pellets **20** are optimal for being loaded into the tube **26** and to be deposited in a biopsy cavity where approximately 1 gram of tissue had been removed. Such a biopsy cavity **40** in a human breast **42** is schematically illustrated in FIG. **7**. The pellets **20** which are loaded into the applicator tube **26** may all include the permanent marker **22**, but it is presently preferred that only every other pellet **20** loaded into the applicator tube **26** have the permanent marker **22**. Such an array of 8 pellets **20**, alternating between pellets with and without permanent markers **22** is shown in FIG. **2**.

[0095] When the pellets **20** are in the tube **26** the piston **28** is extended, as is shown in FIGS. **4** and **5**. The pellets **20** are expelled one-by-one from the tube **26** through the ramp-shaped opening **34** as the piston **28** is pushed into the cylinder or tube **26**. During this process the closed end **36** of the tube

26 is disposed in the cavity **40** formed by biopsy sampling. It is contemplated that the dispersed radio-opaque permanent markers **22** provide a good definition of the entire biopsy cavity **40** for subsequent observation or surgical procedure. FIG. **3** illustrates the applicator device **24** after the pellets **20** have been expelled from the applicator tube **26**.

[0096] FIGS. **8** and **8***a* shows a human breast B which contains a lesion L, such as a mass suspected to be cancerous. An outer cannula **52** has been inserted percutaneously into the lesion L and a biopsy needle (not shown) has been passed through the outer cannula **52** and used to remove a biopsy specimen from the center of the lesion, thereby forming a biopsy cavity BC within the lesion L. After removal of the biopsy needle (not shown), a marker introduction cannula **55** has been passed through the outer cannula such that its distal end **52***d* is located within the biopsy cavity BC. A device **54** for delivering a flowable, detectable marker **50** of the present invention is attached to the proximal end **52***p* of the introduction cannula **55** and is being used to inject a quantity of the detectable marker **50** into the biopsy cavity BC, as shown. FIGS. **9***a*-**9***g*' are schematic, step by step showings of a preferred method for using a detectable marker **50** to mark the site of a lesion L that has been biopsied while the breast B is compressed within a mammography apparatus **56***a* and **56***b*.

[0097] Properties and Functional Requirements of the Detectable Marker

[0098] Preferred Imagable and Instrument-Detectable Embodiments

[0099] The detectable markers **50** of the present invention may be visible on an image created by the particular type or imaging device(s) available during the procedure. In many cases, a form of roentgenographic imaging (e.g., mammography, x-ray, fluoroscopy, CT, etc.) will be used, and the imagable marker **50** will thus comprise a material that is more or less radio-lucent or more or less radiopaque than the tissue surrounding the biopsy cavity (e.g., air, other gas, lipid, oil, a metal salt, barium powder, etc.) such that the marker **50** can be imaged by such x-ray means. In other instances, ultrasound imaging may be used and the imagable marker will comprise a material or substance that has different ultrasound reflective properties (and possible different radiographic density) than the body tissue surrounding the biopsy cavity BC (e.g., air, carbon dioxide, other gasses, saline solution, other liquids, etc.) In other instances, a magnetic imaging technique such as magnetic resonance imaging (MRI) may be used and the imagable marker **50** will comprise a ferromagnetic material or material (e.g., iron powder) having different magnetic density than the body tissue surrounding the biopsy cavity BC.

[0100] Similarly, the marker **50** may be a substance or article that emits energy (e.g., radiation) that is detectable by an instrument (e.g., a gamma detector).

[0101] Preferred Palpable Embodiments

[0102] The preferred palpable embodiments of the invention preferable comprise a substance (e.g., a collagen material as described in U.S. Pat. No. 4,066,083) or an article (e.g., balloon(s), bead(s), etc.) that are sufficient mass to be palpated and located by tactile means while disposed within the biopsy site.

[0103] Preferred Visible Embodiments

[0104] The preferred visible embodiments of the invention may comprise a colored substance such as a dye or colorant (e.g., methylene blue, gentian violet, indigo, dyes used in tattooing, etc.) or colorant particles (e.g., india, indigo, carbon particles or carbon preparations described in Langlois, S. L. P. and Carter, M. L., Carbon Localization of Impalpable Mammographic Abnormalities, Australas Radiol. 35: 237-241 (1991) and/or Svane, G. A Stereotaxis Technique for Preoperative Marking of Non-Palpable Breast Lesions, Acta Radiol. 24(2): 145-151 (1983).

[0105] Preferred Combination Embodiments

[0106] The markers **50** of this invention may combine the attributes of any of the imagable, palpable and/or visible embodiments to provide for detection of the marker **50** by multiple means, such as a) imaging and palpation, b) imaging and visualization, c) imaging, palpation and visualization, or d) visualization and palpation.

[0107] Preferred Residence Time of the Marker at the Biopsy Site

[0108] The detectable markers **10** of the present invention are formulated and/or constructed so as not to move or migrate from the biopsy site when the surrounding tissue is flexed or reconfigured (e.g., as occurs when a breast is decompressed and removed from a mammography machine). Additionally, the detectable markers **10** are formulated and/or constructed to (i) remain present at the site in sufficient quantity to permit imaging and location of the site for at least two (2) weeks after introduction and (ii) clear sufficiently from the site to permit imaging of tissue adjacent to the site, without interference from said detectable marker, at six (6) months after introduction.

[0109] Because the marker **50** is located at, and does not move or migrate from, the biopsy site it serves as a landmark that the surgeon may use to locate and treat or remove the remaining portion of the lesion without having to dissect and explore the surrounding tissue in attempting to locate the lesion. This aspect of the invention is particularly beneficial in cases (such as breast lumpectomy procedures) where it is desired to surgically remove the lesion L with minimal disfigurement, scarring or change in architecture of the surrounding tissue.

[0110] Because the marker **50** remains detectable at the biopsy site for at least two (2) weeks, the commencement of medical or surgical treatment of the lesion L may be delayed for up to two (2) weeks following the removal of the biopsy specimen and the marker **50** will still be present and useable to assist the treating surgeon or other physician in locating and directing treatment to the remaining portion of the lesion. This two (2) week minimum period of residence is especially beneficial in cases where immediate frozen sections can not be read by a pathologist, such as cases of suspected breast cancer wherein a small, non-palpable lesion of the breast has been biopsied by stereotactic biopsy, and the biopsy specimen is sent for routine histopathological evaluation (e.g., fixing, staining and microscopic examination) which takes several days to complete.

[0111] Also, because the marker substantially clears from the biopsy site within six (6) months after its introduction, it will not interfere with or obscure subsequent diagnostic imaging of any remaining portion of the lesion L or the surrounding tissue. This six (6) month maximum residence time of the marker is especially beneficial in cases where the lesion is determined not to be cancerous at present, but presents a risk for future tumorigenesis that warrants periodic imaging of the site of the lesion L and surrounding tissue.

[0112] Embodiments where the Properties of the Marker's Detectable Component Alone Result in Desired Residence Time

[0113] In some embodiments, the detectable marker **10** may comprise a detectable material that has pharmacokinetic properties (e.g., solubility, dissolution, potential for distribution from the biopsy site, potential for local metabolism or break down at the biopsy site) that cause it to remain present at the biopsy site in sufficient quantity to permit imaging of and location of the site for at least 2 weeks after its introduction, while clearing sufficiently from the site to permit imaging of tissue adjacent to the site without interference from said detectable marker, at 6 months after introduction.

[0114] In many applications of the invention, the particular pharmacokinetic or biodistributive property(ies) that determine the rate at which the marker **10** clears from the biopsy site may include its solubility in the interstitial fluids that are present at the biopsy site. In this regard, it has been determined that when the marker **50** is formed of detectable material having a solubility coefficient of less than 1×10^{-3} grams per 100 cubic centimeters of water, such detectable material will typically have the desired detectable residence time within the biopsy site of at least two (2) weeks but not more than 5 to 7 months, and preferably not more than about 6 months. However, it will be appreciated that the detectable residence time of the marker **50** at the biopsy site will additionally vary with the amount of marker **50** material that has been introduced in the biopsy cavity. In this regard, a large volume of a material having a relatively high solubility coefficient can be introduced into the biopsy cavity to ensure that, even though the material has a relatively fast clearance rate, an imagable amount of the material will remain present at the biopsy site at the first time point (e.g., two (2) weeks). On the other hand, a relatively small volume of material having a low solubility coefficient may be introduced into the biopsy cavity and, due to its slow clearance rate, will remain imagable at the biopsy site at the first time period (e.g., two (2) weeks).

[0115] Specific examples of radiographically visible materials that, if introduced into the biopsy site alone, would exhibit the desired detectable residence time (i.e., at least 2 weeks but not more than 6 weeks) include but are not necessarily limited to; AgCl; AgI; $BaCO_3$; $BaSO_4$; K; $CaCO_4$; ZnO; Al_2O_3; and the possible combinations thereof.

[0116] Embodiments with a Clearance Delaying Element to Provide the Desired Residence Time

[0117] In other embodiments, the detectable marker **50** may comprise a detectable material that, if introduced into biopsy site alone, would clear substantially from the biopsy site in less than two (2) weeks after its introduction, thereby failing to provide the desired minimum detectable residence time at the biopsy site of at least two (2) weeks. In such embodiments, the detectable material will be combined (e.g., mixed with, encapsulated by, suspended in, etc.) a clearance delaying element that will cause the detectable material to remain present at the biopsy site in sufficient quantity to permit imaging of and location of the site for at least 2 weeks after its introduction, while still allowing the detectable material to clear sufficiently from the biopsy site to permit imaging of tissue adjacent to the site without interference from said detectable marker, at 6 weeks after introduction.

[0118] Examples of radiographically visible materials that would clear from most biopsy sites in less than two (2) weeks include but are not necessarily limited to; air, gas, lipid, oil, $AgNO_3$; ammonium salts; sodium salts; potassium salts; ethiodized oil (Ethiodol available commercially from Savage Laboratories, Mellville, N.Y., and certain radiographic contrast agents such as iohexyl (Omnipaque, available from Nyegaard-Schering AG, available from Squibb/Bristol Myers.

[0119] Examples of clearance delaying elements that may be combined with the detectable material to form a detectable marker of the present invention include but are not necessarily limited to; polylactic acid; polyglycolic acid; polycaprolactone; an encapsulating membrane surrounding the detectable material.

The following examples are presently preferred formulations for detectable markers **50** of this embodiment:

Formulation 1

Component	Amount
$AgNO_3$	20-70 parts by weight
Polylactic Acid	30-80 parts by weight

Formulation 2

Component	Amount
Ethiodol	10-50 parts by weight
Polyglycolic Acid	50-90 parts by weight

Formulation 3

Component	Amount
Ethiodol	10-70 parts by weight
Topical Thrombin	30-90 parts by weight

Formulation 4

Component	Amount
Polylactic Acid	50-70 parts by weight
Air	30-50 parts by weight

[0120] Form and Consistency of the Detectable Marker

[0121] FIGS. **10***a*-**10***c* illustrate examples of the different possible forms or consistencies of detectable markers **50** of the present invention.

[0122] Flowable Markers

[0123] FIG. **10***a* shows an example of a detectable marker **50***a* of a flowable consistency that is injectable through the lumen of the introduction cannula **55** into the biopsy cavity BC formed within the lesion L. Typically, such flowable markers **50***a* will comprise a dry powder, suspension, or solution. For example, a quantity of dry AgCl powder of 10-1000 micron particle size may be passed through the introduction cannula **55**.

[0124] FIG. **11** shows an example of an injector device **60** that is useable in place of the introduction cannula **55**, to introduce a solid (e.g., powdered, particulate or granular) marker **50** of the present invention into a biopsy site. As shown, this device **60** comprises a non-tapered tubular barrel

61 having a substantially cylindrical inner wall **62** and a plunger **63** that is advanceable within the barrel **61**. A quantity of a solid marker material of this invention is loaded into the barrel **61** of the device **60**, the barrel **61** is inserted into the biopsy site, and the plunger **63** is advanced so as to expel the marker material out of the distal end of the barrel **61** and into the biopsy site.

[0125] Plurality of Beads or Pellets

[0126] FIG. **10***b* shows an example of a detectable marker **50***b* that comprises a plurality of beads or pellets of approximately 10-1000 microns in diameter. Each bead or pellet may itself be formed of detectable material that is biodegradable or otherwise clearable from the biopsy site so as to exhibit the desired detectable residence time as described hereabove such as silver chloride or silver nitrate.

[0127] Alternatively, each bead or pellet may contain a detectable material in its interior and the outer surface of the bead or pellet may be a skin or encapsulating material that is biodegradable such as polylactic acid, so as to provide for the desired detectable residence time within the biopsy site.

[0128] Beads or pellets filled with air, carbon dioxide, or other suitable gas may be used as markers **50***b* of the present invention that are detectable by either ultrasound or x-ray. However, even though such gas-filled markers **50***b* of the present invention are visible on x-ray, they will not obscure or block x-ray imaging of tissue adjacent to the biopsy cavity and, thus, need not biodegrade or clear from the biopsy site by the second time point (e.g., 5-7 months).

[0129] Inflatable Balloon

[0130] FIG. **10***c* shows an example of a detectable marker **50***c* that comprises an inflatable balloon. Such inflatable balloon is passed through the introduction cannula and inflated within the biopsy cavity BC formed within the lesion L. The material of the balloon itself may be detectable and biodegradable or otherwise clearable from the biopsy site so as to exhibit the desired detectable residence time as described hereabove. One example of such a material is polyurethane that has been subjected to hydrolysis in situ. Alternatively, the balloon may contain a detectable material and the balloon itself may form a skin or encapsulating material (e.g., polyurethane) that is biodegradable so as to provide for the desired detectable residence time within the biopsy site.

[0131] Balloons filled with air, carbon dioxide, or other suitable gas may be used as markers **50***c* of the present invention that are detectable by either ultrasound or x-ray. However, even though such gas-filled markers **50***c* of the present invention are visible on x-ray, they will not obscure or block x-ray imaging of tissue adjacent to the biopsy cavity and, thus, need not biodegrade or clear from the biopsy site by the second time point (e.g., 5-7 months).

[0132] Optional Adhesive for Attaching the Marker to Tissue Adjacent the Site

[0133] In any of the above-described embodiments of the invention, the marker **10** may have inherent adhesive properties, or the marker may further comprise an adhesive such as a polyurethane, polyacrylic compound, polyhydroxymethacrylate, fibrin glue (e.g., Tisseal.™.), collagen adhesive, or other biological or biocompatible adhesive that will cause the marker to adhere to tissue adjacent the biopsy cavity BC. Such optional adhesive will further ensure that the marker **10** does not migrate or move from the biopsy site as tissue surrounding the site is moved, flexed, compressed or decompressed.

[0134] Method for Surgical Excision of Tissue Located Adjacent a Biopsy Site

[0135] FIGS. **12***a*-**12***c* show a preferred method for using a visually discernible marker **50** of the present invention to guide the excision and removal of tissues located within a specific band, region or location adjacent the boundaries of the biopsy cavity. As shown in FIG. **12***a*, a visible marker **50** has been introduced into the biopsy cavity BC so as to permit visualization of the boundary BOU of the biopsy cavity BC by the surgeon. Such visualization of the boundary BOU of this biopsy cavity BC can enable the surgeon to selectively remove tissue that is located within a general zone Z_1 of potentially cancerous tissue surrounding the entire biopsy cavity BC (FIG. **12***b*) or within a specific zone Z_2 located on only one side of the biopsy cavity BC (FIG. **12***c*).

[0136] With specific reference to the showing of FIG. **12***b*, the removal of all tissue within a general zone Z_1 surrounding the entire biopsy cavity BC may be desirable in cases where the pathology report has indicated that the previously removed biopsy specimen had no clear margin and, thus, it is desirable to remove all tissue within the zone Z_1 of width X surrounding the biopsy cavity BC on all sides.

[0137] With specific reference to the showing of FIG. **12***c*, the removal of certain tissue within a specific zone Z_2 located to one side of an axis that has been projected throughout the biopsy cavity BC may be desirable in cases where the pathology report has indicated that the previously removed biopsy specimen had clear margins on all but one side and, thus, it is desirable to remove only tissue that is located within the specific zone Z_2 of width X on one side of the biopsy cavity BC.

[0138] The invention has been described hereabove with reference to certain presently preferred embodiments, and no attempt has been made to describe all possible embodiments in which the invention may take physical form. Indeed, numerous modifications, additions, deletions and alterations may be made to the above-described embodiments without departing from the intended spirit and scope of the invention. Accordingly, it is intended that all such additions, deletions, modifications and alterations be included within the scope of the following claims.

What is claimed is:

1. A target tissue localization device for marking a biopsy cavity site comprising: an elongate tubular member having a proximal end, a distal end, and an inner lumen therebetween and at least one bioabsorbable solid body having a radiographically detectable component contained within the inner lumen of the elongate tubular member and bioabsorbable powder within the inner lumen which are collectively configured to at least partially fill the biopsy cavity site when disposed therein.

2. The target tissue localization device of claim **1**, wherein the bioresorbable solid body is remotely imagable by at least one of ultrasound and mammography.

3. The target tissue localization device of claim **1**, wherein the wherein the radiographically detectable component is radiopaque.

4. The target tissue localization device of claim **1**, wherein the at least one bioresorbable body swells upon contact with body fluid.

5. The target tissue localization device of claim **1**, wherein the at least one bioresorbable body swells to substantially fill the biopsy site.

6. A method for marking a biopsy cavity for subsequent remote imaging, comprising:

a. providing a target tissue localization device for marking a biopsy cavity site comprising: an elongate tubular member having a proximal end, a distal end, and an inner lumen therebetween and at least one bioabsorbable solid body having a radiographically detectable component contained within the inner lumen of the elongate tubular member and bioabsorbable powder within the inner lumen which are collectively configured to at least partially fill the biopsy cavity site when disposed therein;

b. removing a biopsy specimen from a breast of a patient, thereby creating a biopsy site; and

c. inserting the at least one bioabsorbable solid body and powder into the biopsy site to at least partially fill and thereby mark the location of the biopsy site.

7. The method of claim **6** wherein the at least one bioabsorbable marker body and powder are collectively configured to at least partially fill the biopsy cavity.

8. The method of claim **7** wherein the at least one bioabsorbable marker body has a detectable first bioabsorbable component with a first bioabsorption rate and a second component mixed with or coating the first component with a second bioabsorption rate different from the first bioabsorption rate.

9. The method of claim **8**, wherein the bioabsorption rate of the first component is greater than the second component.

10. The method of claim **6** wherein the at least one bioabsorbable marker body swells upon contact with body fluid at the biopsy site.

11. The method of claim **6**, wherein the biopsy specimen is tested after removal from the patient.

12. The method of claim **6**, wherein the first component is radiographically detectable.

13. The method of claim **12**, wherein the biopsy site is relocated after the biopsy by detecting the at least one bioabsorbable marker body having a radiographically detectable first component.

14. The method of claim **13**, wherein the bioabsorbable marker body having a radiographically detectable first component is formed at least in part of collagen.

15. The method of claim **13**, wherein the bioabsorbable marker body having a radiographically detectable first component is formed at least in part of gelatin.

16. The method of claim **13**, wherein the bioabsorbable marker body having a radiographically detectable first component is formed at least in part of a polylactic acid.

17. The method of claim **13**, wherein the biopsy site is relocated by detecting the radiographically detectable first component by mammography.

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