(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 December 2006 (28.12.2006)

PCT

(10) International Publication Number
WO 2006/137051 A1

(51) International Patent Classification:
A61N 5/10 (2006.01) *A61M 25/00* (2006.01)

(21) International Application Number:
PCT/IL2006/000668

(22) International Filing Date: 7 June 2006 (07.06.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/691,781 20 June 2005 (20.06.2005) US
60/707,150 11 August 2005 (11.08.2005) US

(71) Applicant *(for all designated States except US)*: **RAMOT AT TEL AVIV UNIVERSITY LTD.** [IL/IL]; 32 Haim Levanon Street, 69975 Tel-aviv (IL).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **KELSON, Itzhak** [IL/IL]; 16 Yelin Street, 62964 Tel Aviv (IL).

(74) Agents: **G. E. EHRLICH (1995) LTD.** et al.; 11 Menachem Begin Street, 52 521 Ramat Gan (IL).

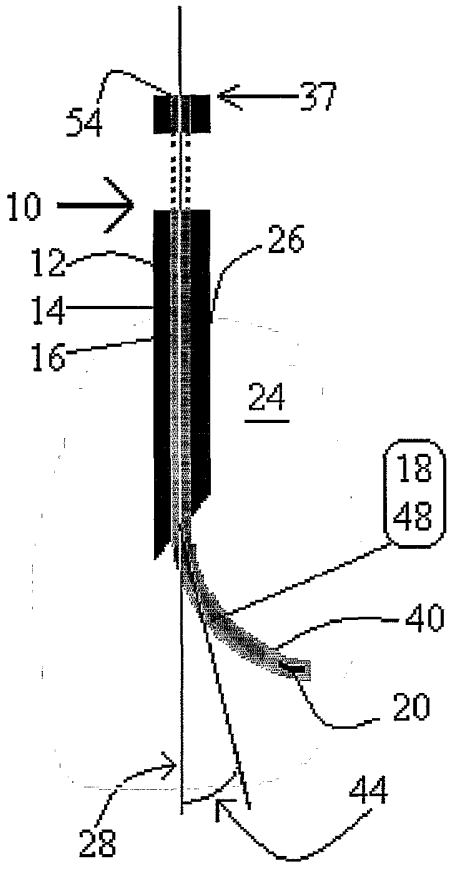
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

[Continued on next page]

(54) **Title:** DEVICE AND METHOD FOR IN-TISSUE POSITIONING OF A SUBSTANCE



(57) **Abstract:** A medical device and method for targeted delivery of a substance into a tissue is provided. The device comprises an elongated housing having a lumen along a length of the elongated housing, and a hollow tubular member capable of substance delivery. The hollow tubular member being positionable within the lumen, wherein the elongated housing and the hollow tubular member are designed such that when a portion of the hollow tubular member is positioned past an orifice of the lumen, the portion protrudes from said lumen at an angle with respect to a longitudinal axis of the elongated housing. The medical device further comprises a mechanism adapted for pushing the substance through the hollow tubular member.

WO 2006/137051 A1

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

DEVICE AND METHOD FOR IN-TISSUE POSITIONING OF A SUBSTANCE

FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to targeted delivery of a substance, and more specifically to a medical device for multiple deliveries of radioactive sources used for brachytherapy treatment of cancerous tissue.

Radiation is used for treating cancer and other diseases of the body. It has been proven that radiation can be used for destroying fast multiplying cells (cancerous), thus hopefully preventing the disease from spreading. While most radiation treatments are delivered with teletherapy, in which the source of radiation is distant from the target, brachytherapy is a form of radiation therapy in which radioactive pellets or seeds are implanted into or near the target tissue to be treated. The most notable example is the case of prostate cancer, where the entire organ is actually irradiated. Complication rates with brachytherapy are minimal, and are more likely to occur in patients who have undergone transurethral resection of the prostate. Otherwise, patients who undergo transperineal implantation show excellent quality of life.

To avoid adversely affecting any healthy region of the subject, one attempts to maximize the dose administered to the target zone (to ensure killing the cancerous cells) while minimizing the dose to other regions (to avoid undesirable damage). It is well known that different types of radiation differ widely in their cell killing efficiency. Gamma and beta rays have a relatively low efficiency. By contrast, alpha particles as well as other heavy charged particles are capable of transferring larger amount of energies, hence being extremely efficient. In certain conditions, the energy transferred by a single heavy particle is sufficient to destroy a cell. Moreover, the non-specific irradiation of normal tissue around the target cell is greatly reduced or absent because heavy particles can deliver the radiation over the distance of a few cells diameters.

On the other hand, the fact that their range in human tissue is less than 0.1 millimeter, limits the number of procedures in which heavy particles can be used. More specifically, conventional radiotherapy by alpha particles is typically performed externally when the tumor is on the surface of the skin.

Because the radioactive sources used in brachytherapy deposit all their absorbed dose within a few millimeters of the source, the sources can be arranged so the radiation dose delivered to adjacent normal tissues is minimized, and the dose delivered to the cancerous tissue itself is maximized. Depositing the radioactive seeds within the cancerous tissue is obtained by inserting a hollow needle or applicator into the target tissue and positioning the radioactive seeds through this channel. The seeds in use may vary in size and composition, but they are invariably rigid objects. Thus, inserting a large number of seeds into a plurality of locations within a cancerous tissue requires a multiplicity of penetration holes to reach that volume, thus causing damage to healthy tissue with each penetration. The most one can do to reduce the number of penetration holes, is to insert a number of seeds collinearly through a single hole.

The use of needles for placing radioactive sources within a cancerous tissue is known, and has been described in the art. For example: US Patent 6648811 to Sierocuk et. al. entitled "Brachytherapy cartridge including absorbable and autoclaveable spacer" teaches a brachytherapy seed delivery system which includes a seed cartridge comprising: a central channel, a plurality of brachytherapy seeds disposed within the central channel and a plurality of absorbable, dimensionally stable spacers disposed within the central channel. This invention is further directed to a method of loading a brachytherapy seed delivery system including the steps of: providing a seed cartridge including a central channel, seeds and spacers as described above; connecting the brachytherapy seed cartridge to a brachytherapy needle including a cannula; and forcing the seeds out of the brachytherapy seed cartridge into the cannula. The present invention is further directed to an improved brachytherapy method including inserting the brachytherapy needle of the brachytherapy seed delivery system recited above into a human organ; and forcing the seeds and the spacer through the cannula of the brachytherapy needle and into the human organ.

Additionally, U.S. Patent No. 6514193 to Kaplan entitled "Method of administrating therapeutically active substance", teaches a method for administering a therapeutically active component including a non-radioactive drug to a target tissue in a subject. The method includes the steps of: (a) providing a brachytherapy seed having a size and shape suitable for passing through the bore of a needle having an interior diameter of less than about 2.7 millimeters (10 gauge); (b) providing a brachytherapy implantation instrument comprising at least one brachytherapy

implantation needle having a bore having an interior diameter of less than about 2.7 millimeters (10 gauge), and being adapted to accept the brachytherapy seed into the bore of the at least one brachytherapy implantation needle and deliver the accepted implantation device into a target tissue; (c) introducing the brachytherapy seed into the bore of the at least one implantation needle of the brachytherapy implantation instrument; (d) introducing at least a portion of the at least one brachytherapy implantation needle into a target tissue in the subject; and (e) actuating the brachytherapy implantation instrument such that the brachytherapy seed is delivered through the bore of the brachytherapy implantation needle into the target tissue.

Furthermore, US Patent 6752753 to Hoskins et. al. entitled "Brachytherapy instrument and method" discloses a brachytherapy instrument and method for delivering therapeutic substances such as radioactive seeds, to internal organs, such as the prostate. The instrument includes a needle and a stylet which are capable of reciprocating relative to one another, but which can be selectively fixed against such movement. The needle is loaded with radioactive seeds, and the stylet advances the seeds to the distal end of the needle.

The prior art described hereinabove do not address the problem of targeted delivery of a plurality of doses to different pre-determined points that are not co-linear. In order to perform such a procedure according to prior art methods and tools, more than one penetration hole must be made, thus damaging the healthy tissue.

There is thus a widely recognized need for, and it would be highly advantageous to have, a device devoid of the above limitations.

SUMMARY OF THE INVENTION

According to one aspect of the present invention there is provided a device for targeted delivery of a substance into a tissue, comprising an elongated housing having a lumen along a length of said elongated housing and a hollow tubular member capable of substance delivery, said hollow tubular member being positionable within said lumen, wherein said elongated housing and said hollow tubular member are designed such that when a portion of said hollow tubular member is positioned past an orifice of said lumen, said portion protrudes from said lumen at an angle with respect to a longitudinal axis of said elongated housing.

According to further features in preferred embodiments of the invention described below, the medical device further comprising a mechanism adapted for pushing the substance through the hollow tubular member.

According to still further features in the described preferred embodiments the mechanism includes a plunger being insertable into the hollow tubular member.

According to still further features in the described preferred embodiments the device is configured for allowing the hollow tubular member to change an azimuthal position with respect to the tissue.

According to still further features in the described preferred embodiments, the elongated housing comprises a substantially tapered tip being designed for allowing introduction of said elongated housing into the tissue.

According to still further features in the described preferred embodiments, the tapered tip is pointed.

According to still further features in the described preferred embodiments, the hollow tubular member is made of a super elastic material.

According to still further features in the described preferred embodiments, the substance is a radioactive source.

According to still further features in the described preferred embodiments, the hollow tubular member is configured as an angled hollow tubular member such that the portion thereof protrudes from the lumen at an angle with respect to the longitudinal axis of the elongated housing.

According to still further features in the described preferred embodiments, the orifice is configured for creating the angle between the longitudinal axis and the portion.

According to still further features in the described preferred embodiments the hollow tubular member further comprises a substantially pointed tip, said tip being designed for protruding through the tissue.

According to still further features in the described preferred embodiments, the orifice is further designed for blocking body fluids from entering into said lumen.

According to another aspect of the present invention there is provided a method for targeted delivery of a substance into a tissue, the method comprising: (a) positioning in the tissue a device comprising: (i) an elongated housing having a lumen along a length of the elongated housing; and (ii) a hollow tubular member capable of

delivering the substance into the tissue; wherein the elongated housing and the hollow tubular member are designed such that when a portion of the hollow tubular member is positioned past an orifice of the lumen, the portion protrudes from the lumen at an angle with respect to a longitudinal axis of the elongated housing; (b) advancing the hollow tubular member within the elongated housing such that the portion thereof is positioned past the orifice of the lumen and in proximity to a first region of the tissue; and (c) delivering the substance to the first region of the tissue through the hollow tubular member.

According to still further features in the described preferred embodiments, the method further comprises changing an azymuthal position of the hollow tubular member with respect to the tissue and delivering the substance to a second region of the tissue through the hollow tubular member.

According to still further features in the described preferred embodiments, changing the azymuthal position of the hollow tubular member with respect to the tissue is effected by retracting the hollow tubular member, repositioning the elongated housing in the tissue and advancing the hollow tubular member within the elongated housing such that the portion of the hollow tubular member is positioned in proximity to the second region of the tissue.

According to still further features in the described preferred embodiments, repositioning the elongated housing in the tissue is effected by rotating the elongated housing about the longitudinal axis.

According to still further features in the described preferred embodiments, changing the azymuthal position of the hollow tubular member with respect to the tissue is effected by rotating the hollow tubular member about the longitudinal axis.

According to still further features in the described preferred embodiments, the hollow tubular member is made of a super elastic material.

According to still further features in the described preferred embodiments step (b) is effected via a plunger positioned within the hollow tubular member.

According to still further features in the described preferred embodiments, the substance is a radioactive isotope.

The present invention successfully addresses the shortcomings of the presently known configurations by providing a medical device for targeted delivery of a plurality of doses to a few pre-determined points that are not co-linear, through a

single penetration hole; thus minimizing damage caused to healthy tissue in the proximity of the tissue to be treated.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. In case of conflict, the patent specification, including definitions, will control. In addition, the materials, methods, and examples are illustrative only and not intended to be limiting.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention is herein described, by way of example only, with reference to the accompanying drawings. With specific reference now to the drawings in detail, it is stressed that the particulars shown are by way of example and for purposes of illustrative discussion of the preferred embodiments of the present invention only, and are presented in the cause of providing what is believed to be the most useful and readily understood description of the principles and conceptual aspects of the invention. In this regard, no attempt is made to show structural details of the invention in more detail than is necessary for a fundamental understanding of the invention, the description taken with the drawings making apparent to those skilled in the art how the several forms of the invention may be embodied in practice.

In the drawings:

FIGs. 1A-1B illustrate a device used for targeted delivery of a substance to a tissue, according to a preferred embodiment of the present invention;

FIGs. 2A-2E illustrate use of the present device in a method of targeted delivery of a substance to a tissue;

FIGs. 3A-3B illustrate the distal end of the elongated housing according to two embodiments of the present invention;

FIGs. 4A-4B illustrate a device used for targeted delivery of a substance to a tissue, according to another embodiment of the present invention;

FIGs. 5A-5C illustrate the use of a guiding sleeve for advancing hollow tubular member according to a preferred embodiment of the present invention;

FIG. 6 illustrates a device for targeted positioning of a plurality of substances within a tissue according to another embodiment of the present invention;

FIG. 7 illustrates a device for targeted positioning of a plurality of doses within a tissue according to yet another embodiment of the present invention.

FIG. 8 illustrates a device used for targeted delivery of a substance to a tissue, according to an additional embodiment of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention is of a medical device for targeted delivery of a substance into a tissue. Specifically, the device enables delivery of a substance to a number of pre-determined sites within a targeted tissue through a single penetration procedure, thus minimizing tissue damage which can result from tissue penetration.

Before explaining at least one embodiment of the invention in detail, it is to be understood that the invention is not limited in its application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments or of being practiced or carried out in various ways. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

Devices for delivery of substances to a tissue are well known in the art, For example, U.S. Patent Nos. 6,648,811 and 6,514,193 describe devices which can be used to deliver radioactive sources to cancerous tissue for brachytherapy treatment. In order to be effective and deliver a plurality of radioactive sources to a number of locations which are not collinear, such devices require an operator to perform more than one tissue penetration thus increasing the likelihood of tissue damage in cases where multiple delivery locations are targeted.

The present invention describes a device designed for specifically addressing this limitation of prior art devices.

Thus, according to one aspect of the present invention there is provided a device for multiple targeted delivery of a substance to a tissue. Examples of substances that can be delivered by the present device include, but are not limited to, imaging markers such as radioactive sources, contrast agents and the like, medicaments used for treating specific tissue regions or tissue ablating substances

used for region specific tissue ablation. Such substances can be delivered to any body tissue in need of treatment or ablation.

Preferably, the substance deliverable by the present device is a flexible radioactive source that is associated with a flexible wire; that is, either the flexible wire is coated with the radioactive source or the radioactive source may be contained within a hollow flexible wire. Examples of a radioactive source which can be used by the present invention include, but are not limited to, is preferably a relatively short lived radio-isotope, such as, but not limited to, Radium-223, Radium-224, Radon-219, Radon-220 and the like, as described in WO 2004/096293 whose disclosure is incorporated herein by reference.

The radioactive source is preferably a relatively short lived radio-isotope, such as, but not limited to, Radium-223, Radium-224, Radon-219, Radon-220 and the like. When Radium 223 is employed, the following decay chain is emitted therefrom:

Ra-223 decays, with a half-life period of 11.4 d, to Rn-219 by alpha emission;

Rn-219 decays, with a half-life period of 4 s, to Po-215 by alpha emission;

Po-215 decays, with a half-life period of 1.8 ms, to Pb-211 by alpha emission;

Pb-211 decays, with a half-life period of 36 m, to Bi-211 by beta emission;

Bi-211 decays, with a half-life period of 2.1 m, to Tl-207 by alpha emission; and

Tl-207 decays, with a half-life period of 4.8 m, to stable Pb-207 by beta emission.

As can be understood from the above decay chain, when Rn-219 is employed as the radioactive source, the decay chain begins with the decay of Rn-219 to Po-215, and continues to Pb-211, Bi-211, Tl-207 and Pb-207.

When Radium 224 is employed, the following decay chain is emitted therefrom:

Ra-224 decays, with a half-life period of 3.7 d, to Rn-220 by alpha emission;

Rn-220 decays, with a half-life period of 56 s, to Po-216 by alpha emission;

Po-216 decays, with a half-life period of 0.15 s, to Pb-212 by alpha emission;

Pb-212 decays, with a half-life period of 10.6 h, to Bi-212 by beta emission;

Bi-212 decays, with a half-life of 1h, to Tl-208 by alpha emission (36 % branching ratio), or to Po-212 by beta emission (64 % branching ratio);

Tl-208 decays, with a half-life of 3m, to stable Pb-208 by beta emission; and

Po-212 decays, with a half-life of 0.3 μs, to stable Pb-208 by alpha emission.

As can be understood from the above decay chain, when Rn-220 is employed as the radioactive source, the decay chain begins with the decay of Rn-220 to Po-216, and continues to Pb-212, Bi-212, Tl-208 (or Po-212) and Pb-208.

When such radioactive sources are positioned in proximity to and/or within the tissue, a plurality of short-lived atoms are released into the surrounding environment and dispersed therein by thermal diffusion and/or by convection via body fluids. The short-lived atoms and their massive decay products (*i.e.*, alpha particles and daughters nuclei), either interact with the cells of the tumor or continue the decay chain by producing smaller mass particles. As will be appreciated by one ordinarily skilled in the art, the close proximity between the radioactive source and the tumor, and the large number of particles which are produced in each chain, significantly increase the probability of damaging the cells of interest, hence allowing for an efficient treatment of the tumor.

The principles and operation of the present device may be better understood with reference to the drawings and accompanying descriptions.

Reference is now made to Figures 1A-1B, illustrating a device for targeted delivery of a substance to the tissue, which is referred to herein as device 10.

Device 10 includes an elongated housing 12 having a lumen 16 running along a length thereof. Device 10 further includes a hollow tubular member 14 that is positionable within lumen 16 and is designed capable of substance 20 delivery. Elongated housing 12 and/or hollow tubular member 14 are designed such that when a portion 40 of hollow tubular member 14 is positioned past an orifice 42 (as seen in Figure 2C) of lumen 16, portion 40 protrudes from lumen 16 at an angle 44 with respect to a longitudinal axis 28 of elongated housing 12.

Elongated housing 12 is fabricated from a biocompatible and preferably rigid material such as stainless steel or Titanium. Elongated housing 12 is preferably cylindrically shaped (i.e., round cross section) and formed as a needle; however, various cross-sectional shapes, e.g. a hexagon, an ellipse, a square and the like are also envisaged. Elongated housing 12 is preferably selected of a cross sectional shape and dimensions which enable smooth translational and rotational motion within a tissue 24 following penetration thereof through hole 26. Elongated housing 12 is fabricated having a length of about 1 – 15 cm and a diameter of about 0.5 – 3.0 mm. Moreover,

elongated housing 12 is designed for penetrating easily into and through tissue 24 by having either a tapered tip 32 or a pointed tip 34 disposed at distal end 36 of elongated housing 12 (as shown in Figures 3A-3B). Tapered tip 32 (or pointed tip 34) is designed for allowing non traumatic introduction of device 10 into tissue 24 thus creating penetration hole 26. Preferably, tapered tip 32 (or pointed tip 34) is an integral part of elongated housing; however, tapered tip 32 (or pointed tip 34) may also be attached to elongated housing 12 at its distal end 36.

Lumen 16 of elongated housing 12 has two or more openings, orifice 42 at or close to distal end 36 of elongated housing 12, and orifice 54 at or close to proximal end 37 of elongated housing 12. Lumen 16 preferably has a diameter of about 0.4 – 3.0 mm and is configured such that hollow tubular member 14 can be positioned and moved within it. Lumen 16 preferably has a circular cross section, although other cross sectional shapes such as a square or an ellipse are also contemplated herein. Hollow tubular member 14 is configured for sliding and rotating within lumen 16 of elongated housing 12. Additionally, hollow tubular member is fabricated for protruding through tissue 24 and thus has a distal end 15 that is either tapered or pointed (see Figures 2E and 4A-5C). Moreover, hollow tubular member 14 is about 1-100 cm long and has an inner diameter of about 0.4 – 3.0 mm so as to enable conduction of substance 20 (preferably radioactive material in the form of seeds) to a tissue.

As is mentioned hereinabove, hollow tubular member 14 and/or elongated housing 12 are designed such that a portion 40 of hollow tubular member 14 protrudes at an angle 44 from longitudinal axis 28 of elongated housing 12 when advanced out of lumen 16 through orifice 42.

To enable angular protrusion, hollow tubular member 14 can be fabricated from a super-elastic material that is angled (has a bend or a kink) in its natural state and forced straight when disposed within lumen 16. An example of a suitable material is NITINOL. Alternatively, hollow tubular member 14 can also be made of a shape memory polymer that can be straight at room temperature and angled at body temperature.

The ability of hollow tubular member 14 to angle when protruding from lumen 16 enables portion 40 to diverge from longitudinal axis 28 when free of lumen 16. Such divergence of portion 40 from longitudinal axis 28 enables a distal end 15 of

hollow tubular member 14 to reach any distance which is smaller than a maximal distance 46 (designated by D in Figure 1B). Furthermore, a trajectory which diverges from longitudinal axis 28 is formed as portion 40 is advanced. The trajectory is set by distal end 15 on which forces are applied on by tissue 24, and the rest of portion 40 simply follows. Moreover, hollow tubular member 14 fabricated from a super-elastic material, when retracted after positioning of the substance, returns to its pre-deployed position and shape while moving along the trajectory but in the reverse direction. It is noted that the divergence of portion 40 is made possible by either having hollow tubular member being naturally straight; and when advanced forward it is deflected while protruding tissue 24 (as described in conjunction with Figures 4A-4B); or by having hollow tubular member 14 having a natural shape of an arc or a helix (or any other shape suitable) which is confined by inner walls of lumen 16 to be straight, and when advanced beyond orifice 42 returns to the natural shape, thus enabling distal end 15 of hollow tubular member 14 to follow the desired trajectory towards pre-determined point 22. While protrusion of portion 40, tissue 24 may apply a resisting force on distal end 15 and or on the sides of hollow tubular member 14. Having the knowledge of all forces applied enables the calculation of the trajectory portion 40 will follow, thus enabling the positioning of substance 20 at pre-determined point 22.

According to one embodiment, portion 40 forms an arc (part of a circle of given radius R), when it protrudes from lumen 16. Thus, deposition of a substance 20 (e.g. radioactive source) follows a circular path of radius R. Furthermore, the maximal distance D, from longitudinal axis 28, Substance 20 can reach is given by $D = 2R$ (as can be seen in Figure 1B). The azimuthal direction of this path is determined by the orientations of rigid elongated housing 12 around its own axis and of hollow tubular member 14 around its own axis. The final placement of substance 20 in its pre-determined point 22 may be effected in two ways which are further discussed herein below in conjunction with Figure 2E.

Angling of hollow tubular member can also be effected by design of housing 12 and positioning of lumen 16 or by use of a guide.

According to another embodiment, hollow tubular member 14 is angled by designing lumen 16 and orifice 42 of elongated housing 12 as illustrated in Figures 4A-4B. Orifice 42 is placed close to distal end 36, and lumen 16 runs straight along the proximal part of elongated housing 12 and is bent towards orifice 42 as it

approaches distal end 36. Advancing hollow tubular member 14 causes it to bend according to the curved part of lumen 16 and thus angled when it is advanced past an orifice 42. In such a configuration, when portion 40 is pushed into a tissue 24, it retains an angled straight direction and thus continues to penetrate the tissue 24 along a straight line forming an angle 44 with longitudinal axis 28.

Hollow tubular member 14 can also be angled by a guiding sleeve 50 which is disposed within lumen 16 (see Figures 5A-5C). Guiding sleeve 50 is configured such that hollow tubular member is deflected and thus angled when it is advanced past an opening 52 of guiding sleeve 50. In such a configuration, when portion 40 is pushed into a tissue 24, it retains an angled straight direction and thus continues to penetrate the tissue 24 along a straight line forming an angle 44 with longitudinal axis 28. This embodiment is further discussed below with respect to Figures 5A-5C.

According to another embodiment, a distal part of hollow tubular member 14 has a natural helical shape when free (as can be seen in Figure 8). Inserting hollow tubular member 14 into lumen 16 causes it to be held straight due to the forces applied by lumen walls of elongated housing 12. When hollow tubular member 14 is advanced forward such that portion 40 protrudes through orifice 42, it returns to its natural shape of a helix.

It is essential for the proper application of the designs described above that the super-elastic element (e.g. NITINOL), used for construction of hollow tubular member 14, return to its original shape after being subjected to the applied strain (either return to an angled shape when free of lumen 16, or return to a linear state when disposed within guiding sleeve 50). For this to be achieved there is a limit on the maximal strain which may be applied δ_{max}, typically of the order of 0.005 – 0.5 Thus the ratio between twice a radius 60 (hereinafter designated as r) of hollow tubular member 14 and a curvature radius 62 (hereinafter designated as R) should not exceed δ_{max} ($2r/R < \delta_{max}$). This limitation is of practical significance only for an embodiment using a guiding sleeve 50 (see Figures 5A-5C), since it imposes a restriction on radius of curvature 62 forced on hollow tubular member 14 by guiding sleeve 50, at a point of deflection 64. Note, that maximal distance 46 from longitudinal axis 28 of elongated housing 12 reached by a curved hollow tubular member 14 is twice the radius of curvature 62, that is $D=2R$.

In order to enable delivery of substance 20 from hollow tubular member 14 to a tissue, device 10 is either attachable to, or further includes a delivery mechanism 18.

Mechanism 18 can be a simple syringe in which case hollow tubular member 14 can be adapted at a proximal end thereof for syringe attachment.

Preferably, mechanism 18 is a plunger 48 which is disposed within hollow tubular member 14 and is designed for pushing substance 20 through and out of hollow tubular member 14 to pre-determined point 22 in a tissue 24. Optionally, plunger 48 is made of a super elastic material as NITINOL or a shape memory material such that it conforms and follows the shape of hollow tubular member 14. Plunger 48 is preferably about 1 - 100 cm long and about 0.1 - 3 mm thick so as to fit within hollow tubular member 14.

Reference is now made to Figures 2A-2E, illustrating use of device 10 in a method of targeted delivery of a substance to the tissue.

Figure 2A illustrates device 10 prior to insertion into tissue 24. At this state: (i) hollow tubular member 14 is retracted and completely contained within elongated housing 12, (ii) mechanism 18 is also at a retracted position, and (iii) substance 20 is at or close to distal end 15 of hollow tubular member 14.

Figure 2B illustrates device 10 inserted into tissue 24 through penetration hole 26. At this stage there is no change in the position of hollow tubular member 14 with respect to elongated housing, and mechanism 18 is still in a retracted position, thus substance 20 remains in its position within hollow tubular member 14. At this stage the azimuthal position of hollow tubular member 14 is adjusted by either rotating elongated 12 about longitudinal axis 28, or by rotating hollow tubular member 14 about longitudinal axis 28, or by rotating both elongated housing 12 and hollow tubular member 14 about longitudinal axis 28.

Figure 2C illustrates device 10 wherein hollow tubular member 14 is advanced so that distal end 15 protrudes through orifice 42 and portion 40 diverges from longitudinal axis 28, thus creating angle 44 with longitudinal axis 28. Additionally, mechanism 18, which may be a plunger 48, is still retracted and therefore substance 20 is contained within hollow tubular member 14 at or close to distal end 15. Furthermore, distal end 15 is at proximity with pre-determined point 22.

Figure 2D illustrates the final step of positioning substance 20 at pre-determined point 22. At this state mechanism 18 has been activated to a deployed state, thus pushing substance 20 out of hollow tubular member 14.

Figure 2E illustrates two manners of transferring substance 20 from distal end 15 of hollow tubular member 14 to pre-determined point 22 within the tissue. In Figure 2E(i) mechanism 18, in this case plunger 48, is advanced forward, thus pushing substance 20 out of hollow tubular member 14. In Figure 2E(ii) mechanism 18, in this case plunger 48, is held fixed while hollow tubular member 14 is retracted with respect to plunger 48. Retraction of hollow tubular member 14 is effected until substance 20 is ejected from tubular member 14 and thus placed at pre-determined point 22. Note that for the method illustrated in Figure 2E(i), substance 20 is preferably made of a solid material thus enabling it to more effectively penetrate tissue 24. The method illustrated in Figure 2E(ii) is applicable to any substance 20 regardless of rigidity.

It is appreciated that multiple dose-positioning may be performed in a few manners. According to a preferred embodiment, a plurality of doses may be inserted into hollow tubular member 14 as described hereinbelow in conjunction with Figures 6 and 7. According to another embodiment a plurality of doses may be positioned by inserting elongated housing 12 and following the steps described hereinabove. When completing the step of positioning substance 20 in pre-determined point 22, it is possible to retract hollow tubular member 14 out while holding elongated housing 12 fixed in its place, and re-inserting either the same or a new hollow tubular member 14 with a new dose of substance 20.

Reference is now made to Figures 4A-4B illustrating a device for targeted delivery of a substance to the tissue, according to another embodiment of the present invention. Orifice 42 is positioned on a side wall close to distal end 36 of elongated housing 12. Additionally, lumen 16 running along longitudinal axis 28 from the proximal end of elongated housing 12 is angled towards orifice 42. Once elongated housing 12 has been positioned in place; hollow tubular member 14, which is initially positioned in the straight part of lumen 16, is advanced towards orifice 42. Advancing hollow tubular member 14 through orifice 42, causes portion 40 to protrude in a straight line that creates an angle 44 with respect to longitudinal axis 28. Advancing

hollow tubular member 14 enables the positioning of substance 20 at pre-determined point 22 after activating mechanism 18.

Reference is now made to Figures 5A-5C illustrating the use of a guiding sleeve for advancing hollow tubular member according to a preferred embodiment of the present invention. Guiding sleeve 50 is fabricated to fit within lumen 16 and to carry hollow tubular member 14 therewithin. By slightly retracting guiding sleeve 50 before and after the insertion of the hollow tubular member 14 into lumen 16, elongated housing 12 is effectively blocked. In this state body fluids cannot penetrate lumen 16 when its content is not there. When elongated housing 12 is inserted through penetration hole 26, guiding sleeve 50 is in a retracted position, as can be seen in Figure 5A, thus preventing hollow tubular member 14 to protrude through an opening 52. Once elongated housing 12 has been positioned in place ready for deploying hollow tubular member 14 for positioning substance 20, guiding sleeve 50 is advanced forward as can be seen in Figure 5B. Advancing guiding sleeve 50 enables the advancement of hollow tubular member 14 through opening 52 and angling of portion 40, thus enabling the positioning of substance 20 at pre-determined point 22 after activating mechanism 18. Figure 5C further shows the combination of using guiding sleeve 50 with hollow tubular member 14 having a circular or a helical natural shape.

Reference is now made to Figure 6 illustrating a device for targeted positioning of a plurality of substances within a tissue according to another embodiment of the present invention.

Elongated housing 12 contains more than one hollow tubular members 14A and 14B (the figure shows two, but more are possible too). Hollow tubular members 14A and 14B are arranged so that they can be advanced separately but it is possible to advance them together. Furthermore, hollow tubular members 14A and 14B are arranged so that they protrude in different directions. This configuration may be used for co-delivering doses of the same substance, or doses of different substances. For example: hollow tubular member 14A can be used for delivering radioactive seeds for brachytherapy treatment at one set of pre-determined points while hollow tubular member 14B can be used for placing a medication such as an anti inflammatory at a different set of pre-determined points.

Reference is now made to Figure 7 illustrating a device for targeted positioning of a plurality of doses within a tissue according to yet another embodiment of the present invention.

The drawing shows a plurality of doses of a substance (indicated by 20A, 20B, 20C, and 20D) arranged in a sequence and ready for positioning at a plurality of pre-determined points 22A, 22B, 22C, and 22D. It is also possible to have each of plurality of doses 20A-20D being different substances to be delivered for treatment as prescribed. It is appreciated that when one dose (for example 20A) is positioned in its pre-determined point (for example 22A), the next dose (for example 20B) is pushed forward within hollow tubular member 14, being ready for positioning in the next pre-determined point (for example 22B).

It is expected that during the life of this patent many relevant brachytherapy substances will be developed and the scope of the term brachytherapy is intended to include all such new technologies a priori.

As used herein the term "about" refers to ± 10 %.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, may also be provided in combination in a single embodiment. Conversely, various features of the invention, which are, for brevity, described in the context of a single embodiment, may also be provided separately or in any suitable subcombination.

Although the invention has been described in conjunction with specific embodiments thereof, it is evident that many alternatives, modifications and variations will be apparent to those skilled in the art. Accordingly, it is intended to embrace all such alternatives, modifications and variations that fall within the spirit and broad scope of the appended claims. All publications, patents and patent applications mentioned in this specification are herein incorporated in their entirety by reference into the specification, to the same extent as if each individual publication, patent or patent application was specifically and individually indicated to be incorporated herein by reference. In addition, citation or identification of any reference in this application shall not be construed as an admission that such reference is available as prior art to the present invention.

WHAT IS CLAIMED IS:

1. A device for targeted delivery of a substance into a tissue, comprising an elongated housing having a lumen along a length of said elongated housing and a hollow tubular member capable of substance delivery, said hollow tubular member being positionable within said lumen, wherein said elongated housing and said hollow tubular member are designed such that when a portion of said hollow tubular member is positioned past an orifice of said lumen, said portion protrudes from said lumen at an angle with respect to a longitudinal axis of said elongated housing.

2. The device according to claim 1, further comprising a mechanism adapted for pushing the substance through said hollow tubular member.

3. The device of claim 2, wherein said mechanism includes a plunger being insertable into said hollow tubular member.

4. The device according to claim 1, wherein said device is configured for allowing said hollow tubular member to change an azimuthal position with respect to said tissue.

5. The device according to claim 1, wherein said elongated housing comprises a substantially tapered tip being designed for allowing introduction of said elongated housing into the tissue.

6. The device according to claim 5, wherein said tapered tip is pointed.

7. The device of claim 1, wherein said hollow tubular member is made of a super elastic material.

8. The device of claim 1, wherein said substance is a radioactive source.

9. The device of claim 1, wherein said hollow tubular member is configured as an angled hollow tubular member such that said portion thereof protrudes from said lumen at an angle with respect to the longitudinal axis of said elongated housing.

10. The device of claim 1, wherein said orifice is configured for creating said angle between said longitudinal axis and said portion.

11. The device of claim 1, wherein said hollow tubular member further comprises a substantially pointed tip, said tip being designed for protruding through the tissue.

12. The device of claim 1, wherein said orifice is further designed for blocking body fluids from entering into said lumen.

13. A method for targeted delivery of a substance into a tissue, the method comprising:

(a) positioning in the tissue a device comprising:

(i) an elongated housing having a lumen along a length of said elongated housing; and

(ii) a hollow tubular member capable of delivering the substance into the tissue;

wherein said elongated housing and said hollow tubular member are designed such that when a portion of said hollow tubular member is positioned past an orifice of said lumen, said portion protrudes from said lumen at an angle with respect to a longitudinal axis of said elongated housing;

(b) advancing said hollow tubular member within said elongated housing such that said portion thereof is positioned past said orifice of said lumen and in proximity to a first region of said tissue; and

(c) delivering the substance to said first region of the tissue through said hollow tubular member.

14. The method of claim 13, further comprising changing an azymuthal position of said hollow tubular member with respect to said tissue and delivering the substance to a second region of the tissue through said hollow tubular member.

15. The method of claim 13, wherein said changing said azymuthal position of said hollow tubular member with respect to said tissue is effected by retracting said hollow tubular member, repositioning said elongated housing in the tissue and advancing said hollow tubular member within said elongated housing such that said portion of said hollow tubular member is positioned in proximity to said second region of the tissue.

16. The method of claim 15, wherein said repositioning said elongated housing in the tissue is effected by rotating said elongated housing about said longitudinal axis.

17. The method of claim 14, wherein said changing said azymuthal position of said hollow tubular member with respect to said tissue is effected by rotating said hollow tubular member about said longitudinal axis.

18. The method of claim 13, wherein said hollow tubular member is made of a super elastic material.

19. The method of claim 13, wherein said step (b) is effected via a plunger positioned within said hollow tubular member.

20. The method of claim 13, wherein the substance is a radioactive isotope.

Figure 1B

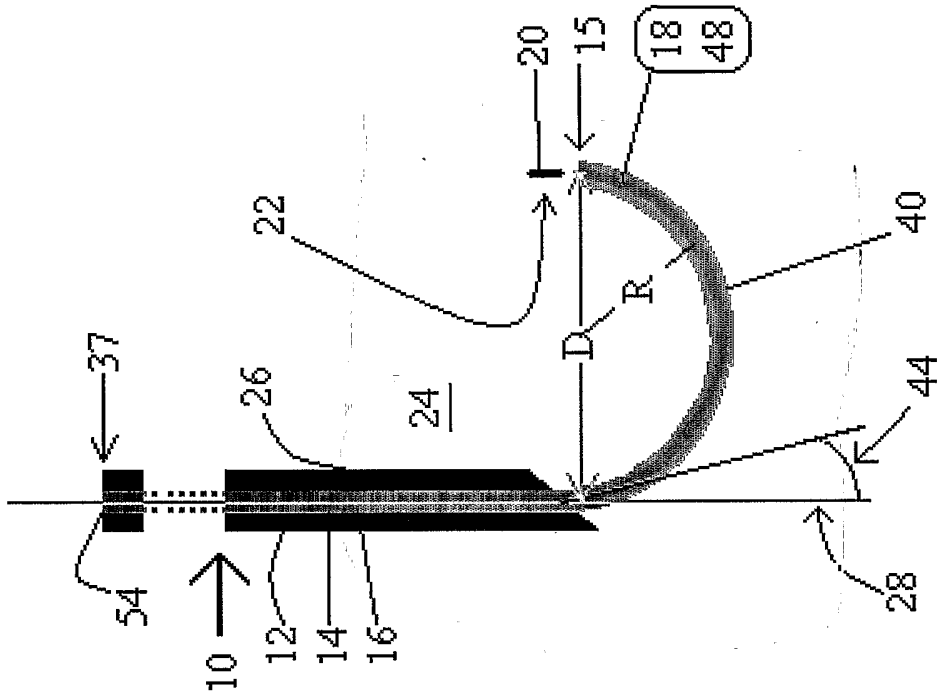


Figure 1A

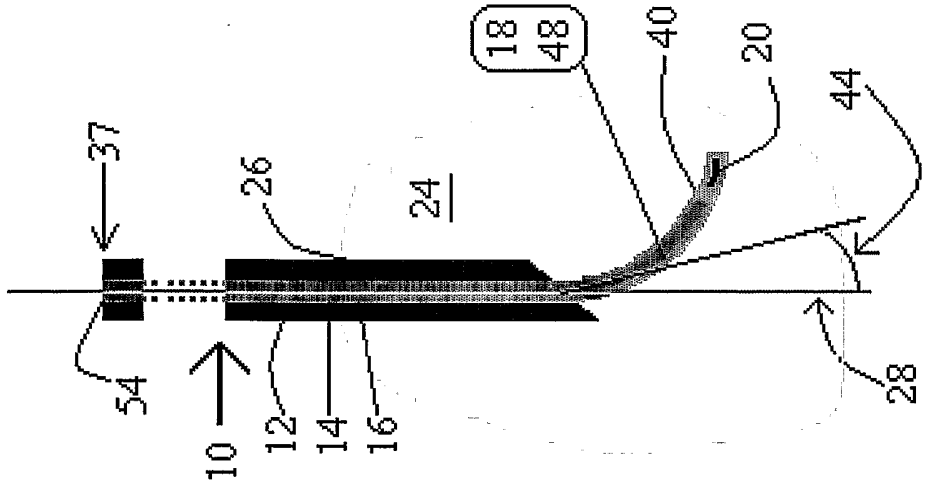


Figure 2A

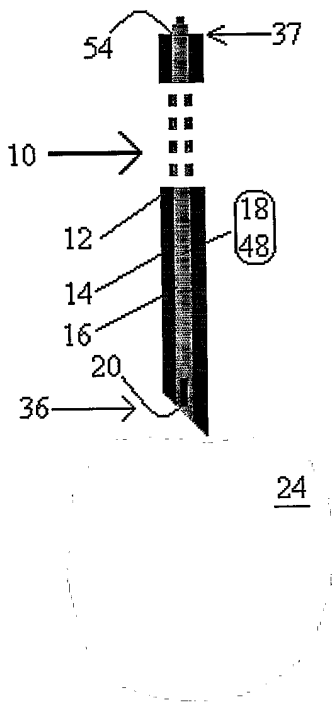


Figure 2B

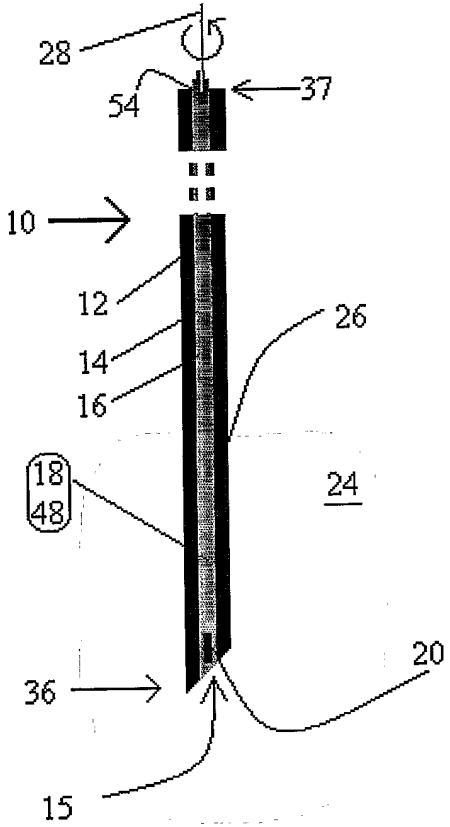


Figure 2C

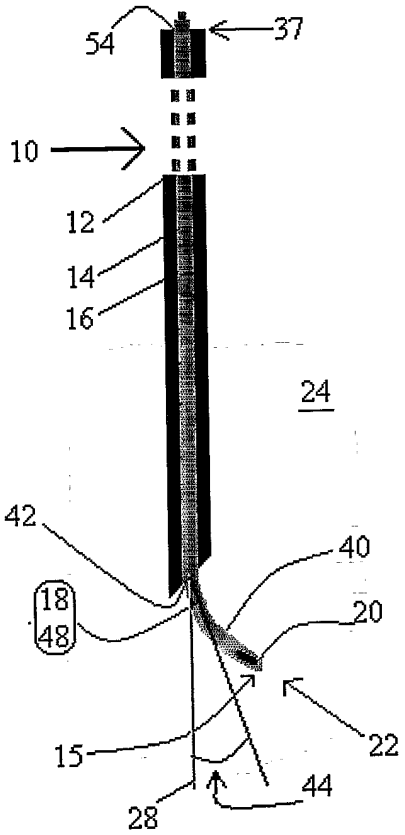


Figure 2D

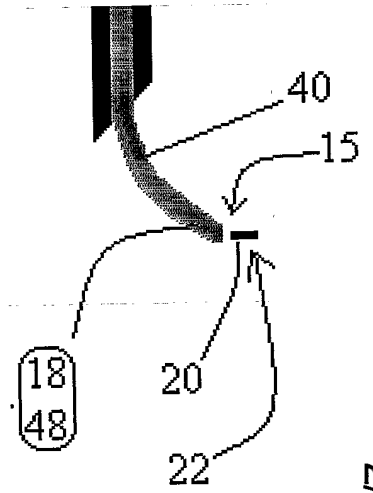


Figure 2E

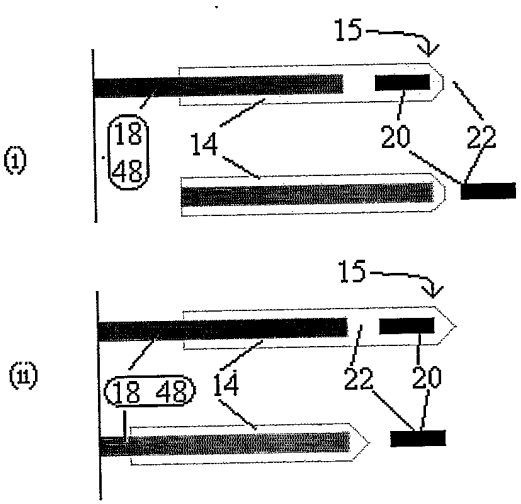


Figure 3B

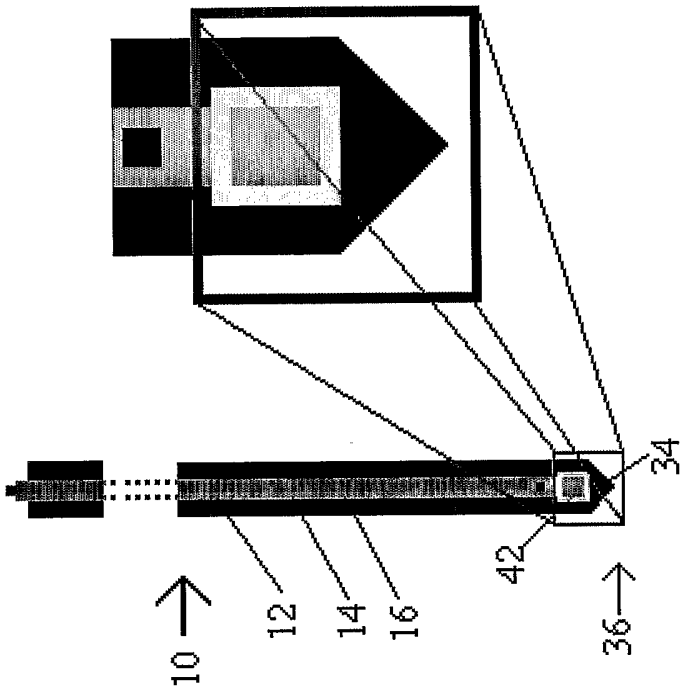


Figure 3A

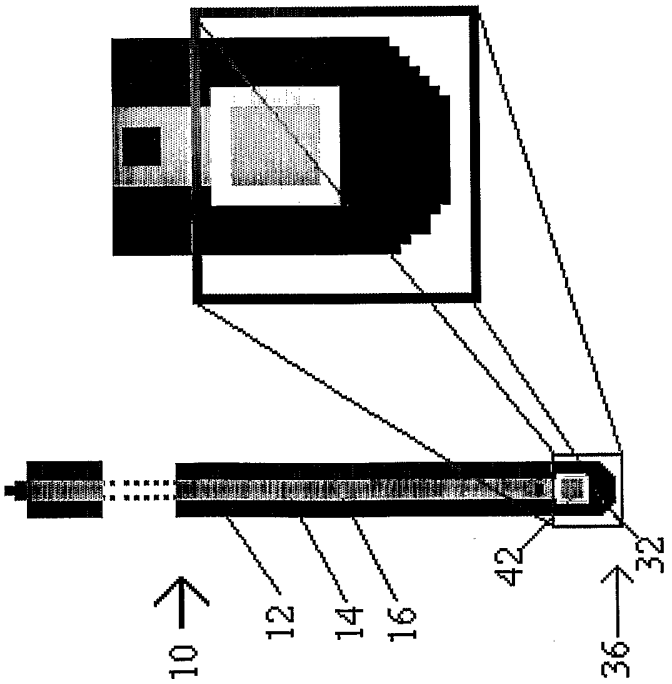


Figure 4B

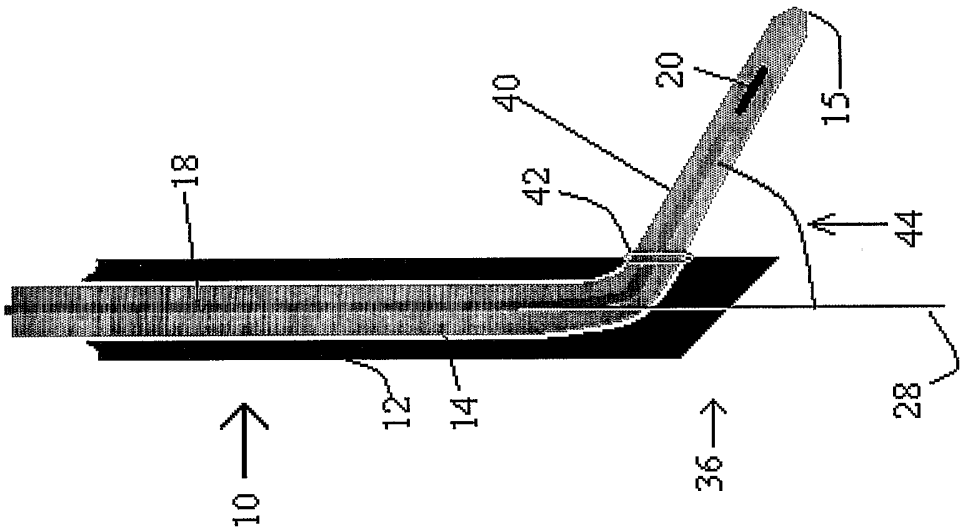


Figure 4A

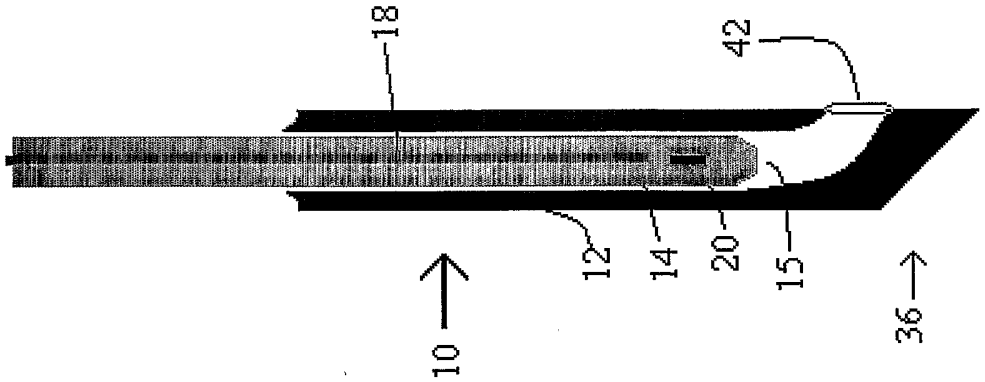


Figure 5C

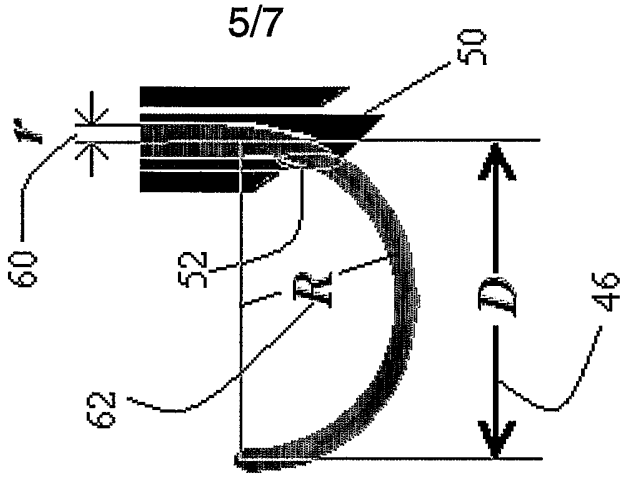


Figure 5B

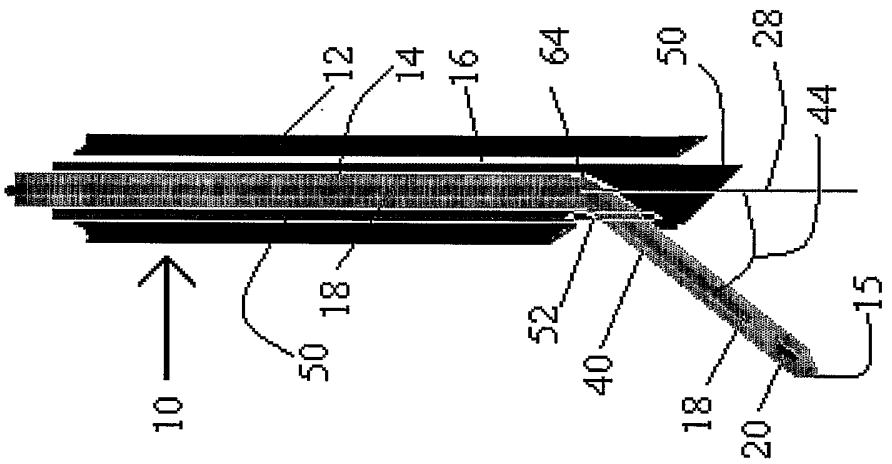


Figure 5A

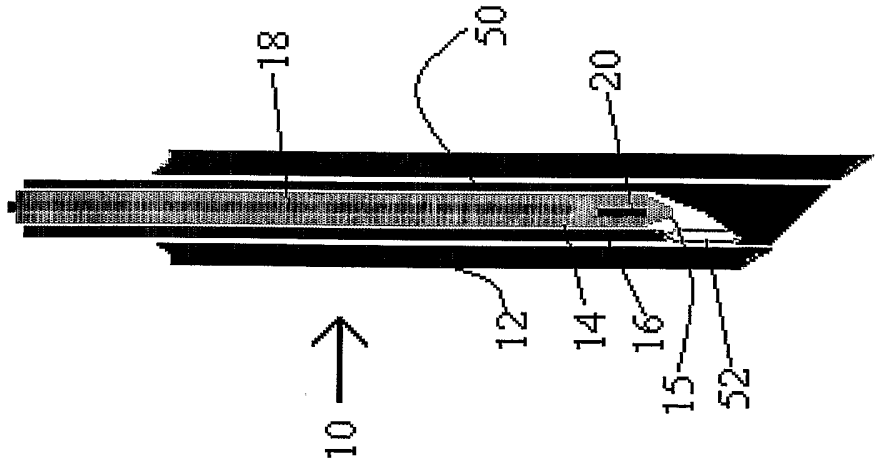


Figure 7

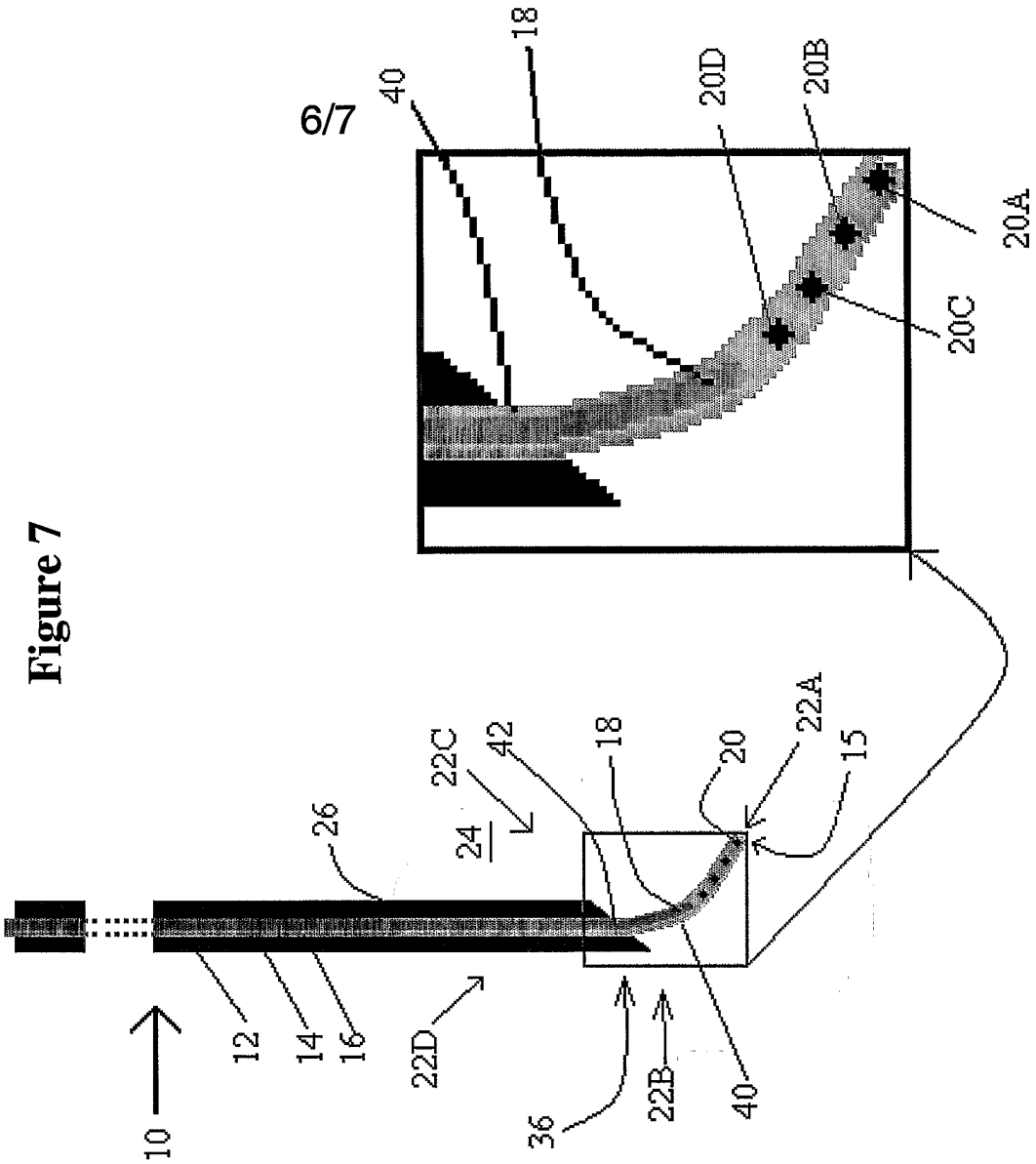
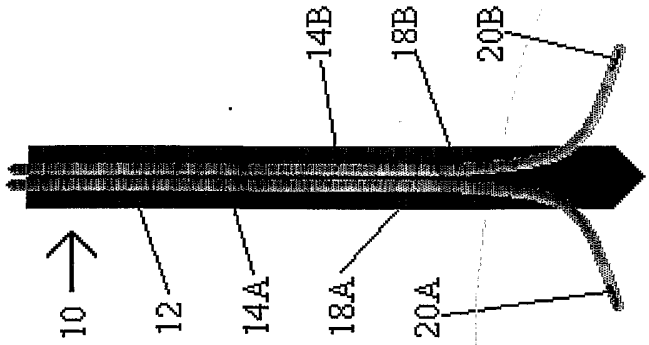


Figure 6



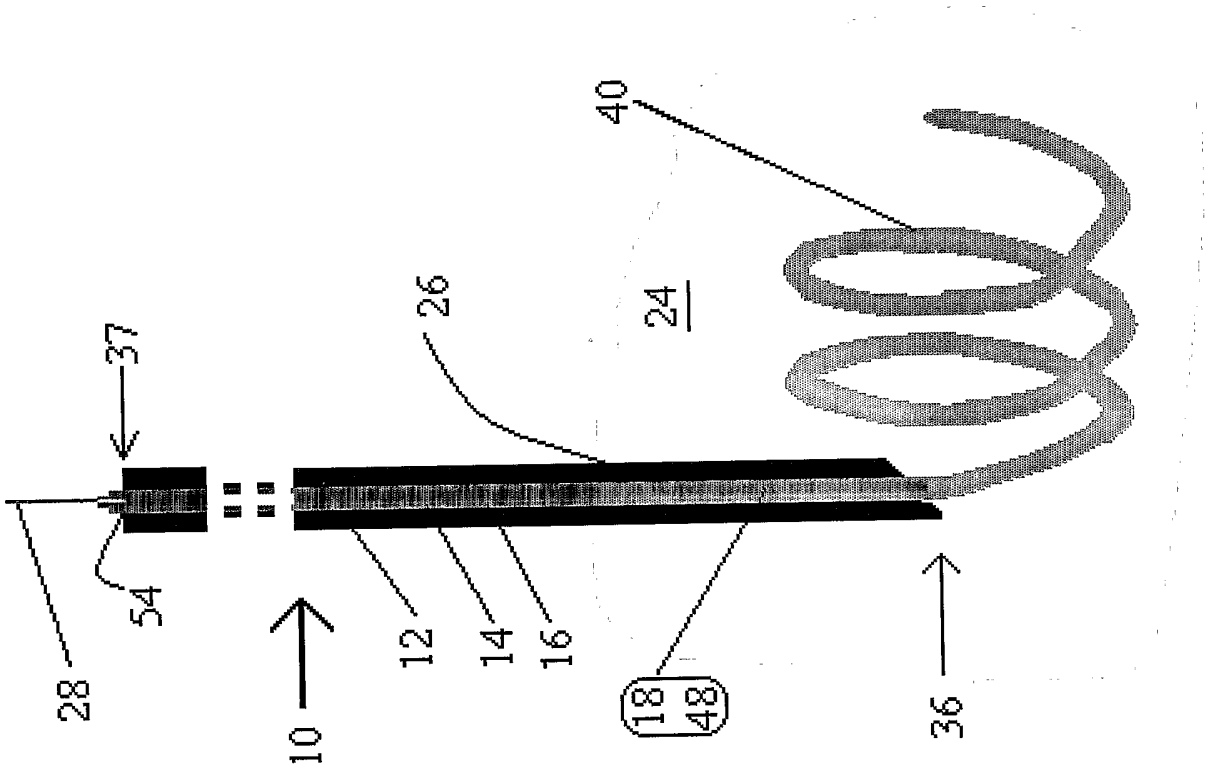


Figure 8

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000668

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N5/10 A61M25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61N A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/085188 A (KAPLAN, EDWARD, J) 31 October 2002 (2002-10-31) page 7, line 7 - page 8, line 2 page 11, line 15 - page 14, line 20; claim 1; figures 3-7	1-12
X	WO 00/40281 A (UNITED STATES SURGICAL CORPORATION) 13 July 2000 (2000-07-13) page 5, line 13 - page 8, line 24	1-4,8-12
X	US 2004/215130 A1 (RIOUX ROBERT ET AL) 28 October 2004 (2004-10-28) paragraph [0051]; figures 10a,10b	1-7,9-12

-/--

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 September 2006	06/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Petter, Erwin

3

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IL2006/000668

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 283 951 B1 (FLAHERTY J. CHRISTOPHER ET AL) 4 September 2001 (2001-09-04) column 8, line 58 - column 9, line 13; figures 1,2 column 10, line 33 - column 11, line 5 column 12, line 45 - line 53 column 16, line 19 - line 44; figures 5a-5d	1-4,8-12
X	US 6 302 870 B1 (JACOBSEN STEPHEN C ET AL) 16 October 2001 (2001-10-16) column 3, line 8 - column 4, line 16; figures 1-3	1-4,8-12
X	US 6 217 554 B1 (GREEN BERT) 17 April 2001 (2001-04-17) column 3, line 33 - column 4, line 56; figures 2a,2b,3a,3b,4a,4b	1-4,8-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IL2006/000668

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13-20
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by surgery and therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IL2006/000668

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 02085188 A	31-10-2002	AU 2002258923 A1	05-11-2002
		US 2002173689 A1	21-11-2002
WO 0040281 A	13-07-2000	AU 760411 B2	15-05-2003
		AU 2846300 A	24-07-2000
		CA 2337132 A1	13-07-2000
		DE 60021330 D1	25-08-2005
		DE 60021330 T2	20-04-2006
		EP 1091777 A1	18-04-2001
		ES 2242602 T3	16-11-2005
		US 2002010439 A1	24-01-2002
US 2004215130 A1	28-10-2004	EP 1603621 A1	14-12-2005
		US 2004186422 A1	23-09-2004
		US 2005020965 A1	27-01-2005
		WO 2004093960 A1	04-11-2004
US 6283951 B1	04-09-2001	AU 1275997 A	11-05-1998
		WO 9816161 A1	23-04-1998
		US 6302875 B1	16-10-2001
		US 2002029079 A1	07-03-2002
		US 6432127 B1	13-08-2002
US 6302870 B1	16-10-2001	AU 4804300 A	17-11-2000
		EP 1173240 A1	23-01-2002
		JP 2002542901 T	17-12-2002
		WO 0066199 A1	09-11-2000
US 6217554 B1	17-04-2001	NONE	