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(54) **OPHTHALMIC TREATMENT APPARATUS**

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See application file for complete search history.

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(57) **ABSTRACT**

A surgical device for localized delivery of beta radiation in surgical procedures, particularly ophthalmic procedures. Preferred surgical devices include a cannula with a beta radiotherapy emitting material at the distal end of the cannula. The surgical device is particularly suitable for use in the treatment of treat Age Related Macular Degeneration (AMD).

36 Claims, 2 Drawing Sheets

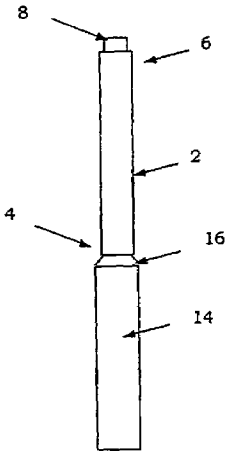

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FIG. 1

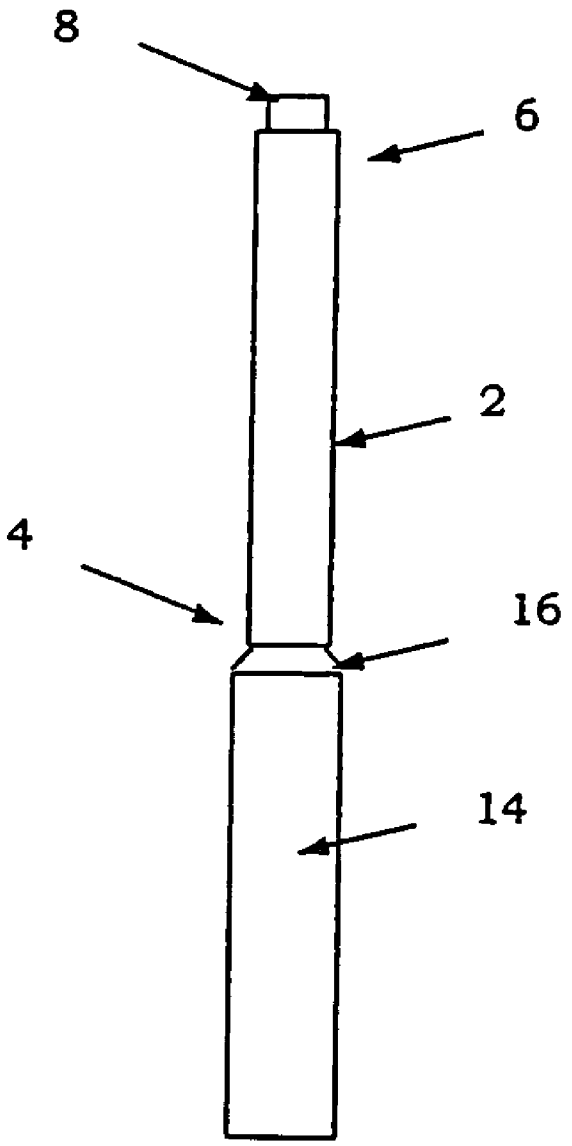
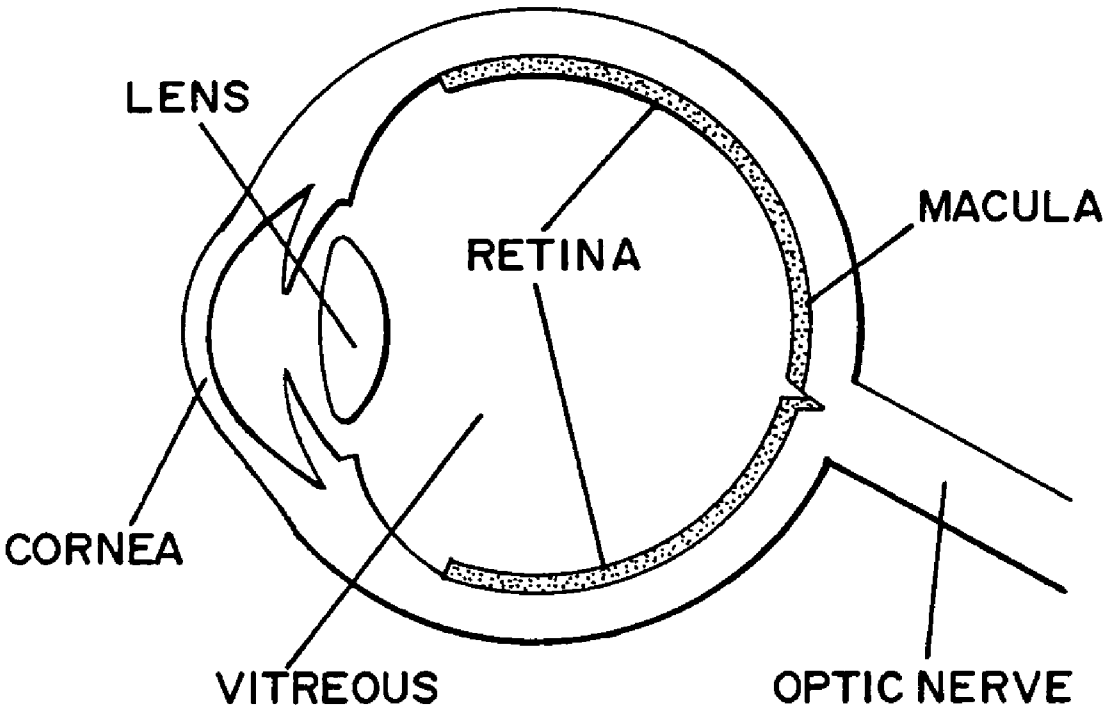


FIG.2



OPHTHALMIC TREATMENT APPARATUS

RELATED APPLICATIONS

This application is a continuation of application Ser. No. 09/790,486, filed on Feb. 22, 2001 now U.S. Pat. No. 6,875,165.

The present invention relates to a device and method for localized delivery of beta radiation in surgical procedures, particularly ophthalmic procedures. More particularly, the present invention relates to a device and method for localized delivery of beta radiation to treat Age Related Macular Degeneration (AMD).

BACKGROUND

The slow, progressive loss of central vision is known as macular degeneration. Macular degeneration affects the macula, a small portion of the retina. The retina is a fine layer of light-sensing nerve cells that covers the inside back portion of the eye. The macula is the central, posterior part of the retina and contains the largest concentration of photoreceptors. The macula is typically 5 to 6 mm in diameter, and its central portion is known as the fovea. While all parts of the retina contribute to sight, only the macula provides the sharp, central vision that is required to see objects clearly and for daily activities including reading and driving Macular degeneration is generally caused by age (Age Related Macular Degeneration, "AMD") or poor circulation in the eyes. Smokers and individuals with circulatory problems have an increased risk for developing the condition.

AMD is the leading cause of blindness in people older than 50 years in developed countries. Between the ages of 52-64 approximately 2% of the population are affected. This rises to an astounding 28% over the age of 75.

The two forms of macular degeneration are known as "wet" and "dry" macular degeneration.

Dry macular degeneration blurs the central vision slowly over time. Individuals with this form of macular degeneration may experience a dimming or distortion of vision that is particularly noticeable when trying to read. In dry macular degeneration, yellowish deposits called drusen develop beneath the macula. Drusen are accumulations of fatty deposits, and most individuals older than 50 years have at least one small druse. These fatty deposits are usually carried away by blood vessels that transport nutrients to the retina. However, this process is diminished in macular degeneration and the deposits build up. Dry macular degeneration may also result when the layer of light-sensitive cells in the macula becomes thinner as cells break down over time. Generally, a person with dry form macular degeneration in one eye eventually develops visual problems in both eyes. However, dry macular degeneration rarely causes total loss of reading vision.

Wet macular degeneration (the neovascular form of the disease) is more severe than dry macular degeneration. The loss of vision due to wet macular degeneration also comes much more quickly than dry macular degeneration. In this form of the disease, unwanted new blood vessels grow beneath the macula (Choroidal Neo-Vascularization (CNV) endothelial cells). These choroidal blood vessels are fragile and leak fluid and blood, which causes separation of tissues and damages light sensitive cells in the retina. Individuals with this form of macular degeneration typically experience noticeable distortion of vision such as, for example, seeing straight lines as wavy, and seeing blank spots in their field of vision. Early diagnosis of this form of macular degeneration is vital. If the leakage and bleeding from the choroidal blood vessels is allowed to continue, much of the nerve tissue in the macula may be killed or damaged, and such damage cannot be repaired because the nerve cells of the macula do not grow back once they have been destroyed. While wet AMD comprises only about 20% of the total AMD cases, it is responsible for approximately 90% of vision loss attributable to AMD.

Currently, Photo-Dynamic Therapy (PDT) is used to treat individuals with wet macular degeneration. During PDT, a photo-sensitive drug is first delivered to the patient's system, typically by injecting the drug into the patient's bloodstream through a vein. The photo-sensitive drug attaches to molecules in the blood called lipoproteins. Because the choroidal blood vessels require a greater amount of lipoproteins than normal vessels, the drug is delivered more quickly and in higher concentrations to the choroidal blood vessels. Next, a non-thermal diode laser light is aimed into the eye to activate the photo-sensitive drug. The activated drug subsequently causes the conversion of normal oxygen found in tissue to a highly energized form called "singlet oxygen." The singlet oxygen, in turn, causes cell death by disrupting normal cellular functions, resulting in the closure of the choroidal blood vessels while leaving normal vessels still functional. While PDT cannot restore vision, it reduces the risk of vision loss by restricting the growth of abnormal choroidal blood vessels.

Laser therapy ("Laser Photocoagulation"), as opposed to Photo-Dynamic Therapy (PDT), uses heat. Basically, a "hot" laser is aimed at the choroidal blood vessels, resulting in the formation of heat when the laser contacts the vessels. This stops the growth, leakage, and bleeding of the choroidal blood vessels. However, the laser destroys surrounding healthy tissue in the process (collateral damage). Further, the "hot" laser forms scars, which may cause blind spots.

PDT, thus, is particularly advantageous because it does not use heat, so less collateral damage results, and the procedure can be repeated as many times as necessary. However, while PDT has shown some efficacy, the population of patients in which it shows efficacy is small (less than 20%). Furthermore, PDT does not typically restore lost vision, but rather, only slows the progression of vision loss. In the attempt to design a selective disruption therapy, it appears that PDT, although groundbreaking, is not aggressive enough to provide satisfying results for affected patients.

Radiation is a promising medical technology that may be effective for the treatment of choroidal neovascularization due to age related macular degeneration. There are basically three types of nuclear radiation: Alpha, Beta, and Gamma.

An alpha particle is simply a helium nucleus. It has the lowest power, penetration, and danger associated with it of the three types of radiation. Several sheets of paper would serve as a shield against alpha radiation.

Gamma radiation is the most powerful, most penetrating, and most dangerous type of radiation. Gamma radiation is an energy wave, not just a particle. Gamma sources are photons. Several meters of rock or many centimeters of lead are required to shield gamma radiation.

Gamma radiotherapy has been shown to be effective in vascular radiation therapy, particularly for the treatment of in-stent restenosis. Randomized data from the Scripps Trial (*The SCRIPPS Trial—Catheter-Based Radiotherapy to Inhibit Coronary Restenosis*; J Invas Cardiol 12(6):330-332 (2000) a randomized, double blind, placebo-controlled study demonstrated a reduction in restenosis rates from 54% in the

placebo group to 17% in patients treated with gamma radiation (^{192}Ir). Gamma sources penetrate human tissues deeply. This makes gamma energy ideal for treating large vessels. Gamma sources have been used in the clinical arena for decades and hospital radiotherapy departments have significant years of experiences using gamma sources.

There are, however, numerous disadvantages to using gamma sources. Photons are not blocked by the "usual" lead shields. A 1 inch lead shield is required. This is usually provided in the form of a very cumbersome heavy lead device attached to rollers that allow it to be wheeled into the catheterization laboratory. Due to the presence of deeply penetrating ionizing radiation, when high-energy gamma radiation is used in the catheterization laboratory, the procedure room must be cleared of all "nonessential" personnel. The patient is observed from a "control room" which is protected by lead shielding. Also, the patient receives more radiation from a gamma radiation procedure as compared to other radiation procedures. The radiation oncologist, who delivers the actual radiation sources, also receives additional radiation exposure. This problem of radiation exposure in the catheterization laboratory environment limits the maximal specific activity of the radiation sources. If the sources are of very high activity, the exposure to health care personnel in the control room will be higher than background exposure. This would be unacceptable. To circumvent this problem, lower specific activity sources must be used. This requires a long dwell time (8 to 20 minutes) to achieve therapeutic doses.

SUMMARY OF THE INVENTION

The present invention provides new surgical devices and methods for use thereof. Devices and methods of the invention are particularly useful for treatment of eye disorders such as Age Related Macular Degeneration More particularly, the present invention provides a device for localized delivery of beta radiation during surgical procedures and methods of use thereof. The device is particularly suitable for the localized delivery of beta radiation for the treatment of macular degeneration. The device delivers beta radiation to the affected sub-macular region afflicted with the condition.

Beta radiation is a high-speed electron. A typical source of beta radiation may be, for example, radioisotope Phosphorus 32 (^{32}P). Beta source electrons only penetrate 1 to 2 mm into human tissue. Even thick plastics easily shield beta energy. The fact that exposure from beta sources is limited allows the specific activity to be much higher than that of gamma sources. This translates into very short dwell times, for example, approximately 3 to 8 minutes of exposure is estimated for ophthalmic applications using a beta source, as opposed to the longer long dwell time associated with the use of a gamma source (8 to 20 minutes). Radiation safety concerns surrounding the use of beta sources are vastly reduced compared to that of gamma radiation. Health care personnel are able to remain in the operating room and additional exposure to the patient and surgeon is negligible. The dose of beta radiation received during macular radiotherapy will be less than that received during a conventional chest x-ray. We have found that beta radiotherapy can be an optimal balance of power, penetration, and safety for many medical applications and specifically for the treatment of choroidal neo-vascularization (CNV) caused by AMD and other diseases of the eye.

In particular, we believe that the exposure of the new blood vessels formed during wet type macular degeneration to the beta radiation provides sufficient disruption of the cellular structures of the new blood cell lesions to reverse, prevent, or minimize the progression of the macular degeneration disease process. Such therapy in accordance with the invention can potentially restore visual acuity, extend retention of visual acuity, or slow the progressive loss of visual acuity.

In a preferred embodiment, the surgical device includes a radiotherapy emitting material positioned on the device, such as a cannula, typically a distal end or portion of the cannula. For added safety, the radiotherapy emitting material is preferably shielded. The cannula may be straight or curved. Preferably, to provide access to the macula from a retinotomy peripheral to the macula, the cannula preferably has a bend or curve. Preferably, the beta radiotherapy emitting material is housed in and partially shielded in the distal end of the cannula by a thin wall metal, such as stainless steel, and/or by a thin wall polymer, plastic, or similar material. The shield may also be designed to be retracted to provide a pathway during the exposure period.

The cannula may have a handle extending its proximal end for providing the surgeon with a better grip on the device and for allowing the surgeon to easily reach the surgical site.

The radiotherapy emitting material preferably emits purely beta radiation, however, the radiotherapy emitting material may also be a material that emits very low and insignificant doses of gamma radiation in addition to beta radiation. Any conventional beta radiation emitting materials used in surgical settings may be used in the present device. For example, some suitable pure beta radiation emitting materials may include: ^{206}Tl (half-life of about 4.20 min), ^{60m}Co (half-life of about 10.47 min), ^{69}Zn (half-life of about 55.6 min), ^{209}Pb (half-life of about 3.253 hours), ^{143}Pr (half-life of about 13.58 days), ^{32}P (half-life of about 14.282 days), ^{33}P (half-life of about 25.34 days), ^{45}Ca (a half-life of about 165 days), ^{90}Sr (half-life of about 28.5 years), ^{99}Te (half-life of about 2.13×10^5 years) and ^{36}S (half-life of about 3.08×10^5 years).

The duration of radiation emission required during a single treatment for Age Related Macular Degeneration using the device can be quite short, e.g. less than 10 or 15 minutes, or even less than 5 minutes. Typical treatments will range from about 1 to 15 minutes, more typically 2 to ten minutes. Thus, for a single-use device, it is possible to use beta radiation emitting materials having short half-lives. However, in some cases, it is desirable to provide a device with a long shelf-life if, for example, the device is not immediately used or if the device is reusable. Thus, in some cases, it is preferred that the beta radiation emitting material is selected from materials that have a half-life of at least about 2 years. Further, when used for the treatment of Age Related Macular Degeneration, it is preferable that the beta emitting material is selected from materials having an energy ranging from about 50 cGr/sec to about 100 cGr/sec.

The present invention also provides device kits, which preferably comprise one or more of the described beta radiotherapy emitting surgical devices, preferably packaged in sterile condition.

Other aspects and embodiments of the invention are discussed infra.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is an isometric view of one embodiment of the surgical device in accordance with the present invention.

FIG. **2** shows a diagram of a normal, healthy eye.

DETAILED DESCRIPTION OF THE INVENTION

Referring now to the various figures of the drawing, wherein like reference characters refer to like parts, there is shown in FIG. **1** a view of a surgical device **1** in accordance with the invention.

In a preferred embodiment, the surgical device **1** includes a cannula **2**, having a proximal end **4** and a distal end **6**. Cannulas are well known and, thus, although described below with reference to a preferred embodiment, the general features (e.g. size, shape, materials) of the cannula **2** may be in accordance with conventional cannulas.

A radiotherapy emitting material **8** is located at the distal end **6** of a cannula **2**. The radiotherapy emitting material **8** preferably emits pure beta radiation because beta radiation is easily blocked and, if not shielded, does not penetrate more than about 1-2 mm in human tissue. However, it is possible to use a radiotherapy emitting material **8** that emits very low and insignificant doses of gamma radiation in addition to beta radiation. For example, some suitable pure beta radiation emitting materials may include: ^{206}Tl (half-life of about 4.20 min), ^{60m}Co (half-life of about 10.47 min), ^{69}Zn (half-life of about 55.6 min), ^{209}Pb (half-life of about 3.253 hours), ^{143}Pr (half-life of about 13.58 days), ^{32}P (half-life of about 14.282 days), ^{33}P (half-life of about 25.34 days), ^{45}Ca (half-life of about 165 days), ^{90}Sr (half-life of about 28.5 years), ^{99}Te (half-life of about 2.13×10^5 years), ^{36}S (half-life of about 3.08×10^5 years).

The half-life of the beta emitting material may vary depending on the use of the device. For example, when used to treat Age Related Macular Degeneration (AMD), one treatment using the device will typically require radiation emission for a period of time ranging from about two to about ten minutes. Thus, single-use devices that are disposed of between treatments may be fabricated using radiotherapy emitting materials **8** with a relatively short half-life. In some circumstances, it is preferable to provide a device having a long shelf-life. In such circumstances, it is preferable to fabricate the device using radiotherapy emitting materials **8** that are continuously active for a very long time (e.g. with a half-life of at least 2 years).

The energy of the beta emitting material may vary depending on the use of the device. For example, when used to treat Age Related Macular Degeneration (AMD), the beta emitting material is preferably selected from materials having an energy ranging from about 50 cGr/sec to about 100 cGr/sec.

Preferably, for added safety during use of the surgical device **1**, the radiotherapy emitting material **8** is at least partially shielded. Because beta radiation is easily shielded, the radiotherapy emitting material **8** may be housed in and partially shielded in, for example, a thin wall metal, such as stainless steel, or by a thin wall polymer, plastic, or similar material. This may be accomplished by providing a thin wall or shield **10** at the distal end **6** of the cannula **2** about the radiotherapy emitting material **8**. In one embodiment, at least a portion of the radiotherapy emitting material **8** is housed in and partially shielded in the distal end **6** of the cannula **2**. Thus, at least a portion of the distal end **6** of the cannula **2** is fabricated of, for example, a thin wall metal, such as stainless steel, or by a thin wall polymer; plastic, or similar material. Alternatively, if desired, the entire cannula **2** may be fabricated of a thin wall metal, such as stainless steel or similar material, or by a thin wall polymer, plastic, or similar material. The shield **10** may also be designed to be retractable to provide further ease in handling the device and shielding of the radiotherapy emitting material **8** when desired.

To provide a surgeon, patient and others in the operating area with adequate protection from the beta radiation, the thickness of the wall or shield **10** or the thickness of the distal end **6** of the cannula in which the radiotherapy emitting material **8** is housed preferably ranges from about 0.5 to about 3 mm, and more preferably, from about 1 mm to about 2 mm. While thicknesses above about 3 mm may be used, it is believed that thicknesses above about 3 mm will not provide significant additional protection from the beta radiation and would make the surgical device **1** bulky and more difficult to handle.

The cannula **2** may have a handle **14** extending its proximal end **4** for providing the surgeon with a better grip on the surgical device **1** and for allowing the surgeon to easily reach the surgical site. Such handles are known and, thus, the handle **14** of the present invention may be in accordance with conventional handles. The handle may be attached to the cannula **2** by a frictional fit and/or conventional fastening means. The connecting means, such as a hub **16** portion may further be included and designed so as to assist in connecting the cannula **2** to the handle **14** via a frictional fit and, if desired, conventional fastening means may be used to assist the hub **16** in connecting the cannula **2** to the handle **14**.

In use, the surgical device **1** is gripped by the handle **14** or a portion of the proximal end **4** of the cannula **2**, and the distal end **6** of the cannula **2** with the radiotherapy emitting material **8** is introduced into the surgical site. In contrast to prior methods in which access to the macula is provided by inserting devices between the eyelid and sclera, the present procedure involves making a standard vitrectomy port incision (typically about a 20 gage—approximately 0.89 mm—incision) in the eye to provide access to the macula, located at the back of the eye. The distal end **6** of the cannula **2** and the radiotherapy emitting material **8** are then inserted through the incision towards the macula. This approach will provide the surgeon with a superior ability to locate the radiotherapy emitting material directly in the affected area. This superior positioning approach provides for more effective therapy and enhanced safety for the lens and optic disc. The surgeon will then perform a vitrectomy and pre-detach the macula by injecting saline beneath the retina with a 41 gage needle to gain "direct access" to the sub macular membrane.

The radiotherapy emitting material **8** is preferably positioned within about 1 mm to about 3 mm of the choroidal blood vessels being treated. In some cases, however, the tip may be placed directly on the choroidal blood vessels.

During the procedure, the surgeon can view the interior of the eye using a standard procedure for viewing the macula through the cornea with an illuminated operating microscope and a lens placed on the cornea. The surgeon can alternatively view the interior of the eye by making a second 20 gage incision to provide access for a fiber optic illuminator, which is a standard practice in retinal surgery.

The cannula **2** is preferably elongate in shape to provide easy access to the surgical site. Preferably, the body portion is designed so as to conform with the incision made in the eye, such that as the cannula **2** is inserted in the eye through the incision, the incision molds around the body portion and prevents leakage around the cannula **2**. Further, the cannula **2** is preferably designed with a smooth surface so as to prevent further trauma to the eye as it is entered through the incision. In one preferred embodiment, as shown in FIG. **1**,

the cannula **2** has an elongate cylindrical shape. The cannula **2** may have a substantially uniform cross sectional diameter or may taper. In one preferred embodiment, the cannula **2** tapers towards the distal end **6** to provide precision in placement of the radiotherapy emitting material **8** and to allow for targeted treatment of only the defective, leaking vessels. Although the cannula **2** is depicted as cylindrical in shape, other shapes may be used as desired. Additionally, the cannula **2** may include a bend to provide enhanced access to areas that are difficult to reach. Preferably, to provide access to the macula from a retinotomy peripheral to the macula, the cannula preferably has a curve.

The dimensions of the surgical device **1** may vary depending on its ultimate use. For example, to treat AMD, in cases where the cannula **2** is inserted into the eye through an incision, the length of the cannula **2** would be designed so that the radiotherapy emitting material **8** would reach the appropriate distance to the back of the eye while allowing only the cannula **2**, and not the hub **16**, handle **14** or other apparatus connected to the proximal end **6** of the cannula **2**, to enter the incision. As such, the portion of the cannula that enters the incision in the eye preferably has a length ranging from about 28 mm to about 32 mm. The radiotherapy emitting material **8** portion of the device preferably has a length that ranges from about 2 mm to about 6 mm. More preferably, the length of the radiotherapy emitting material **8** portion of the device ranges from about 2 mm to about 3 mm. The handle **14** of the device preferably ranges from about 3-6 inches to provide a suitable gripping means for the surgeon. If included, the hub **16**, which connects the cannula **2** to the handle **14**, preferably has a length ranging from about 10 mm to about 12 mm. Further, in applications where a portion of the cannula **2** is inserted into the eye through an incision, the diameter or thickness of the cannula **2** preferably conforms to the size of the incision so that the incision molds around the cannula **2** and prevents leakage around the cannula **2**. For example, in preferred embodiments, the diameter or thickness of the cannula **2** ranges from about 0.6 mm to about 1.2 mm. More preferably, the diameter or thickness of the cannula **2** ranges from about 0.8 mm to about 1.0 mm. However, it is to be understood that the diameter or thickness of the cannula **2** and the length of the portion of the cannula **2** that enters the incision may vary depending on the particular procedure performed, the size of the incision made and the distance from the incision to the treatment area.

The cannula **2** may be fabricated of any conventional materials used in forming similar surgical devices. Preferably, the material is lightweight and strong. Some conventional materials are plastics and stainless steel. Further, because the cannula **2** is inserted in the eye area in some applications, the materials used in forming the cannula **2** must be medically approved for such contact.

The radiotherapy emitting material **8** may be fixedly or removably connected to the distal end **6** of the cannula **2**. Known means such as, for example, adhesives may be used to fixedly secure the radiotherapy emitting material **8** to the cannula **2**. The radiotherapy emitting material **8** may also be removably connected to the cannula **2** by known means such as, for example, forming the radiotherapy emitting material **8** and the cannula **2** to have corresponding threaded portions that allows removable attachment of the radiotherapy emitting material **8** to the cannula **2** so that the device may be reused by simply sterilizing the cannula **2** with ethylene oxide gas or similar means, and replacing the radiotherapy emitting material **8**. Preferably, the entire surgical device **1** is disposed of and replaced between uses to maintain sterility and prevent cross-contamination between uses.

The present invention also includes kits that comprise one or more beta radiotherapy emitting surgical devices of the invention, preferably packaged in sterile condition. Kits of the invention may also include written instructions for use of the beta radiotherapy emitting surgical devices and other components of the kit.

The foregoing description of the invention is merely illustrative thereof, and it is understood that variations and modifications can be effected without departing from the scope or spirit of the invention as set forth in the following claims. For example, although the present invention is described in detail in connection with ophthalmic surgical procedures, particularly in connection with the treatment of AMD, the present invention is not limited to use on the eye. Rather, the present invention may be used on other areas of the body to treat various conditions such as, for example, the prevention of restenosis.

What is claimed is:

1. An intra-ocular ophthalmic surgical device for use in radiotherapy treatment of tissue of the eye, comprising:

a cannula having a proximal end portion and a distal end portion, said cannula sized for insertion of the distal end portion into the vitreous chamber of a human eye;

a radiotherapy emitting material cooperatively associated with the distal end portion of the cannula during the radiotherapy treatment of the eye tissue, said cannula being adapted to allow positioning of the radiotherapy emitting material at a selected location within the vitreous chamber spaced from the tissue to be treated during radiotherapy treatment thereof.

2. The device of claim **1** wherein the distal end portion of the cannula is tapered.

3. The device of claim **1** further including a shield at least partially shielding the radiotherapy emitting material.

4. The device of claim **1** wherein the cannula has a diameter between about 0.6 mm to about 1.2 mm.

5. The device of claim **1** wherein the cannula comprises a length of about 28 mm to about 32 mm.

6. The device of claim **1** wherein the cannula includes a curve to provide access to the macula.

7. The device of claim **3** wherein the distal end portion of the cannula comprises the shield.

8. The device of claim **3** wherein the shield comprises metal.

9. The device of claim **3** wherein the shield at least partially shields the radiotherapy emitting material so that the radiotherapy emitting material is exposed to only a selected localized area of the eye.

10. The device of claim **9** wherein the selected localized area comprises sub-retinal tissue.

11. The device of claim **10** wherein the sub-retinal tissue comprises blood vessels.

12. The device of claim **1** wherein the radiotherapy emitting material has an energy sufficient to provide a dose rate from between about 50 cGy/sec to about 100 cGy/sec.

13. The device of claim **1** wherein the radiotherapy emitting material comprises a beta radiation emitter.

14. The device of claim **1** wherein the radiotherapy emitting material comprises a pure beta emitting therapeutic component.

15. The device of claim **1** wherein the radiotherapy emitting material has sufficient energy to treat neovascularization.

16. The device of claim 1 wherein the cannula has a radiotherapy emitting material portion having a length between about 2 mm and about 3 mm.

17. The device of claim 1 wherein the radiotherapy emitting material is disposed within the distal end portion of the cannula.

18. The device of claim 1 in which the cannula has a diameter between about 0.8 and 1.0 mm.

19. The device of claim 1 wherein the radiotherapy emitting material has an energy sufficient to provide a dose rate greater than or equal to about 50 cGy/sec.

20. The device of claim 1 wherein the radiotherapy emitting material cooperatively associated with the distal end portion of the cannula is at least partially housed within the cannula.

21. The device of claim 1 wherein the radiotherapy emitting material cooperatively associated with the distal end portion of the cannula is fixedly or removeably associated with the distal end portion of the cannula.

22. The device of claim 3 wherein the shield and the radiotherapy emitting material are relatively moveable.

23. An intra-ocular ophthalmic surgical device for radiotherapy treatment of tissue of the eye, comprising:

a proximal end portion and a distal end portion, said distal end portion sized for insertion into the vitreous chamber of an eye;

the distal end portion of the surgical device including a radiotherapy emitting material cooperatively associated therewith so that radiation is emitted from the distal end portion of the surgical device to radioactively treat eye tissue; and

a shield at least partially shielding the radiotherapy emitting material and configured to allow radiation emitted from the distal end portion of the surgical device to be exposed to target eye tissue.

24. The device of claim 23 wherein the radiotherapy emitting material is disposed in the distal end portion of the device.

25. The device of claim 23 wherein the target eye tissue comprises sub-retinal tissue.

26. The device of claim 25 wherein the sub-retinal tissue comprises blood vessels.

27. The device of claim 23 wherein the radiotherapy emitting material has an energy sufficient to provide a dose rate from between about 50 cGy/sec to about 100 cGy/sec.

28. The device of claim 23 wherein the radiotherapy emitting material comprises a beta radiation emitter.

29. The device of claim 23 wherein the radiotherapy emitting material comprises a pure beta emitting therapeutic component.

30. The device of claim 23 wherein the radiotherapy emitting material has sufficient energy to treat neovascularization.

31. The device of claim 23 wherein the radiotherapy emitting material and the shield are relatively moveable.

32. The device of claim 23 in which the device comprises a cannula that has a diameter between about 0.6 mm to about 1.2 mm.

33. The device of claim 23 in which the device comprises a cannula that has a diameter between about 0.8 and 1.0 mm.

34. The device of claim 23 wherein the radiotherapy emitting material has an energy sufficient to provide a dose rate greater than or equal to about 50 cGy/sec.

35. The device of claim 23 wherein the radiotherapy emitting material cooperatively associated with the distal end portion of the device is at least partially housed within the device.

36. The device of claim 23 wherein the radiotherapy emitting material cooperatively associated with the distal end portion of the device is fixedly or removeably associated with the distal end portion of the device.

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BRACHYTHERAPY

The MammoSite™ breast brachytherapy applicator: A review of technique and outcomes

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ABSTRACT The MammoSite™ breast brachytherapy device was designed to overcome the potential scheduling problems associated with external beam radiotherapy (EBRT) and the technical difficulties of multi-catheter-based interstitial brachytherapy. The device consists of a silicone balloon connected to a catheter which contains an inflation channel and a port for passage of a high-dose-rate brachytherapy source. The American Brachytherapy Society and American Society of Breast Surgeons have published partial breast irradiation (PBI) patient selection guidelines. The MammoSite™ applicator has been shown in two dosimetric studies to treat a comparable volume to multicatheter-based interstitial implants. The MammoSite™ catheter can be placed at the time of lumpectomy or in a separate procedure using ultrasound guidance. Four optimization methods have been described: the single point method, the six prescription point method (RUSH Technique), the University of Southern California Norris Cancer Center Method, and the Surface Optimization Technique. An excellent or good cosmetic outcome has been reported in 80% to 93% of patients at 1 year in most studies. Cosmetic results appear highly related to skin spacing. The MammoSite™ applicator has been associated with early side effects comparable with traditional breast conserving therapy. A NSABP trial will randomize patients to either whole breast irradiation or PBI consisting of interstitial brachytherapy, MammoSite™ brachytherapy, or 3D conformal radiation. © 2005 American Brachytherapy Society. All rights reserved.

Keywords: MammoSite™; Brachytherapy; Breast cancer

Introduction

Large trials with extended follow-up have shown that breast conserving therapy (BCT) offers equivalent overall survival to modified radical mastectomy in patients with early stage breast cancer (1, 2). Studies have also shown that in certain parts of the United States, as few as 10% of eligible patients receive BCT (3, 4). One of the reasons patients do not undergo BCT relates to the time commitment of 6–7 weeks of external beam radiation (EBRT).

Numerous institutions use multi-catheter based implants to deliver partial breast irradiation (PBI). With the use of these techniques, the radiation dose can be delivered to the patient in 1 week or less. This offers patients potentially improved quality of life and avoids many of the scheduling difficulties associated with EBRT. A recent publication reported similar rates of local control between highly selected patients treated with interstitial brachytherapy and matched patients who underwent EBRT at the same institution (5). In addition, the early results of Radiation Therapy Oncology Group (RTOG) 9517 were reported at the 2004 American Society of Clinical Oncology (ASCO) annual meeting. At a median follow up of 3.7 years, the breast recurrence rate was found to be only 3% in patients treated with PBI (6). Several other studies have also reported excellent rates of local control (7–9) while a few others have not (10, 11).

Interstitial implants using multiple catheters require additional training and expertise. These implants are not offered at many institutions across the United States. The catheter insertion may be a potentially painful procedure for patients to endure due to the numerous puncture sites required. In addition, the catheter sites can lead to decreased cosmetic outcome and infection if optimal techniques are not employed.

The MammoSite™ brachytherapy device was designed to simplify the brachytherapy procedure and avoid the technical and logistic problems of multi-catheter based interstitial

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brachytherapy. The MammoSite™ device consists of a silicone balloon connected to a catheter (see Fig. 1). The catheter contains an inflation channel and a port for passage of the high-dose-rate brachytherapy source. The balloon is inflated with saline solution mixed with a small amount of radiographic contrast to aid in visualization. An ^{192}Ir source, connected to a computer-controlled high-dose-rate (HDR) remote afterloader, is inserted into the balloon to deliver the prescribed dose of radiation. The prescription dose is 34 Gy given in 10 fractions of 3.4 Gy per fraction, b.i.d., with a minimum of 6 hours between daily fractions. A CT scan is performed to insure a minimum balloon to skin distance of 5 mm (preferably 7 mm) and optimal conformance of the breast tissue to the surface of the balloon.

Patient selection

Outside of an IRB approved protocol, it is important to limit PBI to patients who are at a low risk for failure outside the area of the lumpectomy cavity. Large retrospective reviews have shown that the incidence of failures outside the tumor bed is infrequent in certain subsets of patients with early stage breast cancer. Also, failure outside the lumpectomy bed does not appear to be affected significantly by the use of whole breast EBRT (12, 13) although data supporting either conclusion are incomplete. This leads to the conclusion that the main effect of radiation is to prevent recurrence in the tumor bed. Thus, radiation focused just to the area of the lumpectomy cavity should provide equivalent results to EBRT in certain subsets of patients.

The American Brachytherapy Society (ABS) and the American Society of Breast Surgeons (ASBS) have published conservative patient selection criteria in an attempt to select patients who would be at a minimal risk for recurrence after treatment with PBI (14, 15). The ABS and ASBS selection criteria are listed in Table 1. The percentage of patients presenting for BCT who would be eligible for PBI using the ASBS guidelines was examined by Pawlik *et al.* (16). The authors of this study found that only 122 out of 443 patients (27.4%) met all five selection criteria. This issue still remains controversial.

Recommendations on which PBI patients might benefit more from a multi-catheter based interstitial implant than a MammoSite™ implant have not yet been clarified in the literature. Factors considered at our institution include cavity size, cavity geometry, and margin status. A lumpectomy cavity that is not large enough to accommodate an inflated 30 cc balloon is not ideal for a MammoSite™ implant. If the balloon is inflated to a volume less than 30 cc, the physician runs the risk of not treating an adequate margin of breast tissue. In addition, a cavity which is very non-spherical, such as a linear cavity or a highly asymmetrically shaped cavity, is more likely to lead to a MammoSite™ implant with poor conformance or asymmetry of the catheter. If the MammoSite™ applicator is placed at the time of lumpectomy, the cavity should be examined by both the surgeon and radiation oncologist. If the surgeon determines that the cavity can be modified without affecting cosmetic outcome, it is our belief that attempts should be made to make the cavity larger or more spherical. However, this has not been supported by any published data. If cosmetic outcome would be adversely affected by modifying the cavity, strong consideration should be given to treating the patient with a multi-catheter based implant. When a cavity is determined to be inadequate during an ultrasound-guided closed cavity implant, we perform the implant with interstitial needles rather than attempt to modify the cavity. Margin status is also considered at our institution when evaluating a patient for PBI. A patient with margins 1 mm or less may be better served by a multi-catheter implant than a MammoSite™ implant. Interstitial needles allow a little more flexibility in shaping the dose around an area at an increased risk for recurrence than a MammoSite™ implant using multiple dwell positions and prescription points. Again, these observations are based upon our clinical experience. There are little data describing the most optimal PBI technique to use in each clinical situation and the optimal margin required for successful PBI has not been established.

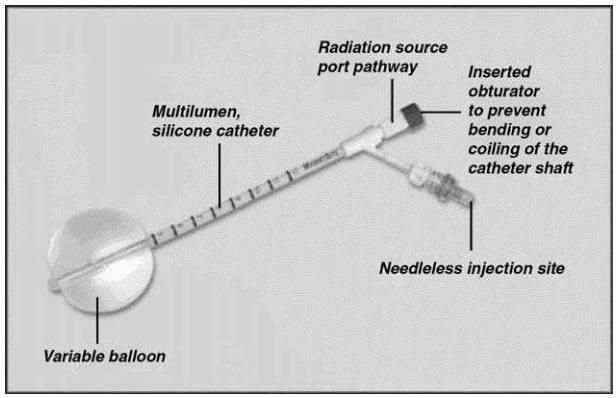

Fig. 1. MammoSite™ brachytherapy device. (Reprinted, with permission, from Proxima Therapeutics, Inc.)

Table 1
The American Brachytherapy Society (ABS) and American Society of Breast Surgeons (ASBS) patient selection criteria for partial breast irradiation

	ABS Recommendations	ASBS Recommendations
Age	45 years	50 years
Histology	Unifocal, invasive ductal carcinoma	Invasive ductal carcinoma or DCIS
Tumor size	3 cm	2 cm
Surgical margins	Negative microscopic Surgical margins of excision	Negative microscopic Surgical margins of excision of at least 2-mm
Nodal status	N0	N0

Volume of treatment

It is an important point for the MammoSite™ applicator to treat a comparable volume of tissue to that of interstitial multi-catheter-based implants to produce comparable results. A study by Dickler *et al.* (17) addressed this question by comparing CT scans of the same patient with the empty lumpectomy cavity and CT scans with the inflated balloon. The volume of the PTV was calculated and then an equivalent volume around the empty lumpectomy cavity was constructed. It was found that the volume of breast tissue treated by the MammoSite™ device was equal to the volume encompassed by a mean 1.6 cm margin around the lumpectomy cavity (17). This is comparable to multi-catheter-based methods which treat a margin of tissue 1–2 cm around the surgical cavity. Edmundson *et al.* (18) published the first article describing the dosimetric characteristics of the MammoSite™ applicator. The mean PTV of the MammoSite™ patients was 112.1 cm^3 compared with 98.3 cm^3 for patients treated with multi-catheter-based interstitial brachytherapy at the same institution. Despite these findings, it is also important to remember that the optimal volume of clinically uninvolved breast tissue surrounding the lumpectomy cavity that requires RT for the successful application of PBI has not been established.

Implant technique

The MammoSite™ applicator can be placed either at the time of lumpectomy or post lumpectomy using an ultrasound-guided technique. Gittleman *et al.* (19) reported the results of 106 cases from 25 institutions and found that 62% of the catheters were placed using an open technique at the time of lumpectomy while 38% were placed using a closed cavity with ultrasound guidance. Keisch *et al.* (20) found no association between catheter placement technique and cosmetic outcome.

The advantages of placing the catheter at the time of lumpectomy include the convenience of a one-time procedure, the ability to modify an inadequate cavity at the time of catheter insertion, and a decreased interval between the end of surgery and start of radiation. A disadvantage of open cavity placement is that final pathology is not known at the time the MammoSite™ catheter is placed. This can necessitate removal of the device secondary to positive margins. Other concerns with open cavity placement leading to device removal include inadequate skin spacing and suboptimal conformance. The exact rate of device removal due to these issues is uncertain at this time (see below).

The catheter can be placed post lumpectomy using ultrasound guidance either through the lumpectomy scar or a separate incision. Zannis *et al.* (21) described the postoperative ultrasound guided technique. The authors of this article advocate placing the MammoSite™ applicator postoperatively, because it allows careful selection of patients and leads to less catheters being removed. At our institution, we place the MammoSite™ catheter both at the time of lumpectomy and after the lumpectomy using ultrasound guidance. When the catheter is placed after the lumpectomy, we attempt to minimize the amount of time between lumpectomy, catheter placement, and the start of radiation.

After the catheter is placed, CT scans are used to assess the quality of the implant. A minimum balloon to skin distance of 5 mm is suggested but clinical data supporting the safety of this recommendation are lacking at the present time. A distance of at least 7 mm is highly advised at this time until more published data are available. In addition, conformance of the balloon to the cavity should be assessed. At our institution, we determine conformance by quantifying the amount of the PTV that is encompassed by air cavity or seroma. If greater than 10% of the PTV is composed of fluid or air, conformance is considered to be inadequate. The catheter is either removed or the patient has a repeat CT to evaluate whether the amount of fluid or air has diminished enough to allow adequate treatment. It is important to remember that these recommendations are not yet supported by clinical outcome data. The symmetry of the balloon in relation to the catheter should also be evaluated. Implants in which the lumen is located asymmetrically can lead to underdosage of tissue around the cavity. With the use of multiple prescription point, multiple dwell position methods, efforts can be made to compensate for areas that receive inadequate dose. However, these recommendations are also not yet supported by published clinical data.

The percentage of patients not receiving MammoSite™ brachytherapy due to inadequate implants has been reported in several studies. Keisch *et al.* (22) reported that 9 out of 70 patients (12.9%) treated in a multi-institutional study had the catheters pulled due to inadequate implants. Seven were removed for poor conformance and 2 were removed for close skin spacing. Dowlatshahi *et al.* (23) reported that 9 out of 129 (7.0%) patients treated at 3 institutions had inadequate implants. Six were removed due to close skin spacing and 3 patients had poor conformance. The exact rate of device removal due to inadequate implants remains unresolved at this time.

Dosimetric techniques

Single point technique

A publication by Edmundson *et al.* (18) first described a single prescription point, single dwell position technique. In this technique, the PTV is defined as a 1-cm expansion from the balloon surface using the chest wall and skin as limiting structures. A single prescription point is placed 1 cm from the balloon surface on a perpendicular line which bisects the catheter axis. This technique does not account for the lack of PTV coverage due to source anisotropy. Also, the use of only a single prescription point and single dwell position, does not allow isodose lines to conform to the shape of the PTV. Thus, the complex 3-D shape the balloon

takes once it is inflated and conforms to the surrounding tissue is not accurately described.

Six prescription point, multiple dwell position technique (RUSH technique)

To correct for the shortcomings of the single point method, our institution developed the six prescription point, multiple dwell position technique (RUSH Technique) (17). In this technique, six optimization points are placed 1 cm from the balloon surface. Four points are placed in a plane transverse to the balloon axis perpendicular to the axis of the catheter and two points are also placed along the axis of the catheter. By providing more optimization points, this technique is able to more accurately conform the isodose lines to the shape of the balloon. In addition, the prescription points along the axis of the catheter are able to compensate for the source anisotropy.

The six prescription point, multiple dwell position method was compared with the single point technique in a previous publication by Dickler *et al.* (17). The six point method was found to improve dose coverage compared with the single point technique. The mean V90 (percentage of the volume receiving 90% of the prescription dose) for the six point method was 97.2% vs. 89.5% for the single point method. The mean V100 (percentage of the volume receiving 100% of the prescription dose) for the six point method was 88.9% vs. 77.6% for the single prescription point technique. This was at the cost of a slightly decreased dose homogeneity index (DHI) of 0.62 vs. 0.66 for the six-point and single-point methods respectively.

University of Southern California Norris Cancer Center method

Astrahan *et al.* published an optimization method developed at the Norris Cancer Center (24). This method uses a CT-based planning system to account for source anisotropy and limit the toxicity to the skin. Like the six point method, this technique uses multiple optimization points and multiple dwell positions. The authors of this study showed that by varying the number and arrangement of dwell positions, the shape of the isodose lines could be modified. In this method, the position and number of the optimization points varies for each patient depending on the shape of the inflated balloon and the distance to the skin. This is in contrast to the RUSH Technique, in which the position and number of optimization points remain the same from patient to patient.

Surface optimization technique

Although the RUSH Technique and the University of Southern California Norris Cancer Method compensate for source anisotropy, they do not completely describe the complex 3-D structure of the inflated MammoSite™ balloon. The Surface Optimization Technique was developed by our institution to improve upon the techniques described above (25). Using CT images, the surface technique attempts to conform the 100% isodose line to the surface of the PTV. With the use of a customized software program, hundreds of optimization points are distributed on the surface of the PTV. The source dwell times and positions are then optimized to equalize the dose delivered to each of these points. Once optimized, the dwell times are normalized to deliver 3.4 Gy per fraction to the prescription point 1 cm from the balloon surface.

The advantages and disadvantages of each optimization method are listed in Table 2. At our institution we currently use the six prescription point, multiple dwell position method (RUSH Technique) to treat patients with the MammoSite™ breast brachytherapy applicator. We feel that this optimization method offers the best compromise between a method that accounts for source anisotropy, partially accounts for the 3-D shape of the inflated balloon, and a method that is not technically difficult to utilize.

As can be seen from the above discussions, the optimal dosimetric technique for dose specification remains controversial. Additional data and clinical follow-up will be required to help ascertain the advantages and/or disadvantages of each method and the optimal means of dose delivery.

Effect of contrast in the balloon

The dose perturbation caused by radiographic contrast in the balloon was described in a publication by Kirk *et al.* (26). In this article, the authors quantified the dose perturbation as a heterogeneity correction factor (HCF) based on the radii of the inflated balloon and the concentration of the contrast in the balloon. For a typical implanted balloon, the HCF values decrease from .992 for 6% contrast concentration to .902 for 100% contrast concentration. This would correspond to an almost 10% reduction in dose in balloons inflated with high concentrations of radiographic contrast. The authors recommend that the amount of radiographic contrast used be minimized and monitored carefully to avoid potential reductions in dose to the PTV. At our institution, we use only 1–2 cc of radiographic contrast mixed with approximately 30–70 cc of saline in the balloon.

Cosmetic outcome

The cosmetic outcome of patients treated with the MammoSite™ brachytherapy applicator has been reported in previous publications. Keisch *et al.* (20) reported the 2-year results for 43 patients treated as part of a multi-institutional trial. With a median follow-up of 21 months, 88% of all patients were found to have an excellent or good cosmetic outcome. Skin to balloon spacing of greater than 7 mm was associated with improved cosmetic outcome.

Our institution reported the single institution results for 30 patients at a median follow up of 13 months (27). Ninety-three percent of the patients achieved an excellent or good

Table 2
Advantages and disadvantages of the optimization methods for the MammoSite™ breast brachytherapy applicator

Method	Advantages	Disadvantages
Single Point Technique	• Technically simple • Reproducible	• Does not compensate for source anisotropy • Does not account for the 3-D shape of the inflated balloon • Single dwell position
Six Prescription Point, Multiple Dwell Position Technique (RUSH Technique)	• Compensates for source anisotropy • Partially accounts for 3-D shape of inflated balloon • Position of prescription point relative to balloon surface remains the same	• Six prescription points do not completely describe the 3-D shape of the inflated balloon
University of Southern California Norris Cancer Center Method	• Compensates for source anisotropy • Partially accounts for 3-D shape of inflated balloon	• Requires customization of method for each individual patient
Surface Optimization Method	• Attempts to completely account for 3-D shape of balloon • Compensates for source anisotropy	• Technically more difficult compared with other methods

cosmetic outcome. Excellent cosmetic outcome was associated with a greater balloon-to-skin distance, lower maximal skin dose per fraction, and smaller mean balloon volumes. Due to the small number of patients, these results did not achieve statistical significance.

Other studies have reported the early cosmetic outcome to be excellent or good in 80% to 93% of patients (23, 28, 29).

Shah *et al.* (29) compared the cosmetic outcome between patients who received multi-catheter-based interstitial brachytherapy and patients who received brachytherapy with the MammoSite™ applicator. The study reported that the MammoSite™ applicator was associated with significantly less subcutaneous fibrosis compared with interstitial brachytherapy. However, when only patients who did not receive chemotherapy were compared there was no significant difference in any parameter of cosmesis except Grade 1 erythema, which was seen more often in the patients treated with the MammoSite™ catheter (29).

Clearly, additional follow-up will be required to validate the long-term stability of these early cosmetic results. Previous data with EBRT suggest a minimum of 3 years is required for cosmetic results to stabilize after treatment.

Complications

Overall, the MammoSite™ brachytherapy applicator appears to be very well tolerated based upon the limited published data. Keisch *et al.* reported mostly very mild side effects related to the device placement (20). Mild erythema occurred in 57.4%, breast pain in 42.6%, and dry desquamation in 13% of the patients treated. The few significant side effects included seromas in 11.1%, moist desquamation in 5.6%, and infection in 3.7% of the patients. Richards *et al.* (28) reported the results of 32 patients treated at St. Vincent Cancer Center. The authors of this study reported that bright erythema and patchy moist desquamation occurred in 25% of patients treated.

Dickler *et al.* (27) reported an infection rate of 13.3% in 30 patients treated in a single institution study. The rate of infection did not appear to be associated with track length (the length of catheter located beneath the skin of the patient's breast) or the use of systemic chemotherapy. Richards *et al.* (28) reported an infection rate of 16% in 32 patients. If significant rates of infection persist in future studies, consideration should be given to the use of prophylactic antibiotics.

Despite these encouraging early results with toxicity, it will be important to validate these observations in controlled studies and at multiple other institutions.

Discussion

PBI is supported by the in-breast failure patterns reported in studies which included both patients who received EBRT and patients who did not receive EBRT after lumpectomy. These studies have shown that the incidence of failures outside the tumor bed is infrequent in certain subsets of patients with early stage breast cancer. In addition, failure outside the lumpectomy bed does not appear to be significantly affected by whole breast EBRT (12, 13).

The MammoSite™ and other methods of PBI offer an alternative to whole breast irradiation. PBI delivers a high dose of radiation to the area most at risk for recurrence and limits the radiation dose to the surrounding normal breast and adjacent tissues. Potential advantages of PBI compared with whole breast EBRT include shorter overall treatment time and improved quality of life. Non-randomized trials using multi-catheter-based implants have shown excellent clinical results with PBI (5–9).

The MammoSite™ breast brachytherapy applicator was developed to simplify the breast brachytherapy procedure and make it more accessible to patients. The catheter can be placed at the time of lumpectomy or with the use of ultrasound guidance in a separate procedure after lumpectomy. Studies have been performed which show that the MammoSite™ applicator treats a similar volume to an interstitial multi-catheter technique (17, 18). Early results regarding complication rates and cosmesis have been favorable (20, 22, 23, 27–29). However, to date, there have been no long-term results reported on patients treated with the MammoSite™ applicator. In addition, a large randomized trial comparing EBRT to multi-catheter interstitial brachytherapy has yet to be published.

The upcoming NSABP trial will randomize patients between EBRT and PBI. The PBI arm will consist of interstitial brachytherapy, MammoSite™ brachytherapy, or 3-D conformal PBI (30). The schema and eligibility requirements of the proposed trial are shown in Fig. 2. The results of this trial have the potential to provide a definitive answer regarding the benefits of PBI, and hence lead to more women undergoing BCT.

Conclusion

Until the NSABP trial results are available, strict patient selection criteria such as the recommendations advocated by the ABS and ASBS should be followed. In addition, quality assurance of brachytherapy implants is of utmost importance. We believe that the extrapolation of the results from previous studies on multi-catheter-based interstitial implants, early favorable results with the MammoSite™ applicator, and the potential advantages of the MammoSite™ catheter, including accessibility and improvement in a patient's quality of life, justify its use in appropriate patients with early breast cancer. Future studies will further define subgroups that will benefit from the MammoSite™ breast brachytherapy catheter.

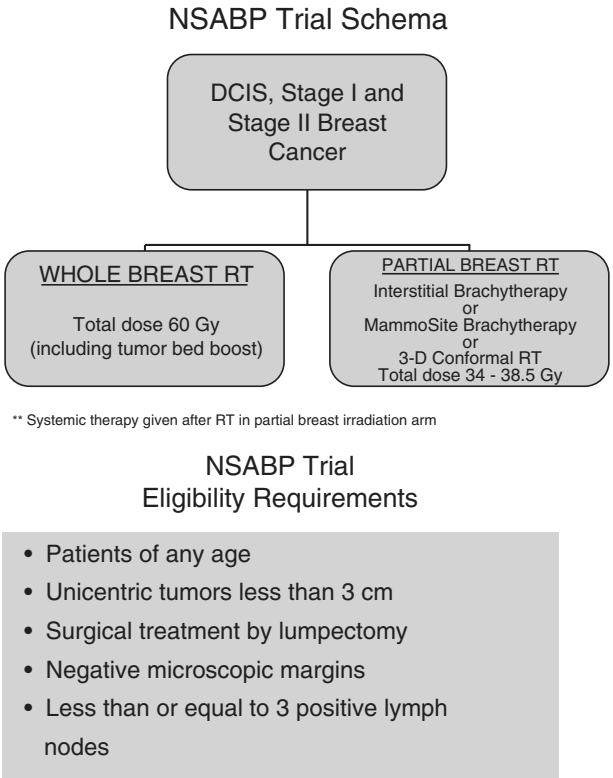

Fig. 2. Schema and eligibility for NSABP trial.

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