Treatment Planning for IVBT: Clinically desirable radiation dose distributions and evaluation of competing dose distributions

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1. Introduction

The potential usefulness of vascular radiotherapy to prevent restenosis has rapidly developed from positive preclinical studies carried out in animals in the 80's and 90's to a large number of clinical trials which are underway in both United States and Europe in 1998.[1-12] Trials are currently underway which encompass varying treatment techniques (Temporary and Permanent Implants), varying source preparations (sealed and non-sealed sources), various isotopes and a variety of delivery methods. The importance of radiation dose and it's relationship to outcome has been demonstrated by numerous authors in this field in both the preclinical and clinical areas. Although there are certainly other factors beyond dose which determine outcome, it is incumbent upon researchers in this field to understand thoroughly the relationship between the prescribed dose, the dose delivered and the benefits and side-effects of treatment.

This presentation briefly describes the methods of measurement and dose calculation focussing on the unique needs of vascular radiotherapy. The effect of curvature of the source train, source centering and the effect of guidewires and metallic endoprosthesis on the dose distribution will be presented. The American Association of Physicists in Medicine (AAPM) has contributed greatly to standardization of dose prescription and reporting through the establishment of Task Group 60. This group is continuing their work such that future developments in vascular radiotherapy will be attended by new standards. Conventional radiation therapy has in the modern era involves precise calculation of dose and superimposition of those dose distributions on appropriate anatomical images. This technology may be applied to vascular radiotherapy and examples of early work in this field by our group at Emory University will be presented.

2. Dose Measurements

In vascular brachytherapy, the distribution of radiation dose around the source is difficult to measure because the sources have very small diameters and the dose distribution must be determined close to the source (< 5 mm). The dose gradient is very steep and the radiation detection instrument must therefore have a small volume. TLDs have been used for some of the early measurements; however, the more recent studies have used plastic scintillators and radiochromic film. Radiochromic film provides some very desireable properties for this application ie. good spatial resolution (0.1 mm), linearity, energy independence and tissue equivalent. Radiochromic film has been used in the characterization of both catheter-based and stent radiation delivery devices. For catheter-based techniques, the dose rate of a source/source train at various distances from the source center have been measured/determined by the manufacturer and this information is used for calculating the treatment times. The dose rate of the source must be traceable to a NIST standard. For radioactive stents the manufacturers have simply specified the activity of the stent at the time of shipping and not provided dose-rate information because of the complex geometry of the stent. The end-user is expected to use the stent when it is between certain activity levels.

3. Dose Calculation Methods

Calculation of the dose within a specified volume is a standard means employed by radiation oncologists/radiation physicists for planning teletherapy (external) or brachytherapy treatments. These dose calculation methods provide clinicians with a tool to make pre-treatment evaluations of the dose distribution and customize the treatment for the individual patient. In vascular radiotherapy, use of dose calculation methods for pre-treatment evaluation is not widely carried out at this time.

Dose calculation methods can be grouped into Monte Carlo methods and semi-empirical methods. Monte Carlo dose calculation methods use physical interaction principles to calculate the dose distribution of an irradiated medium. Even though Monte Carlo can be very accurate it is generally not used because of the amount of time required to get an accurate answer. Instead, most dose calculation involves the use of tabulated data generated from dose measurements or Monte Carlo calculations to perform a very fast and generally accurate assessment of the dose distribution.. To determine the dose distribution around a radioactive source simply requires inputting the physical location and activity of the source.

Calculation of the dose at distances of 5 mm or less from a radioactive source is something that most dose calculation programs are not set up to handle. For vascular brachytherapy, AAPM TG-60 has presented a standardized method for calculating the dose distribution around beta-emitting and gamma-emitting catheter-based systems (seeds and wires) . This task group has not yet provided recommendations for calculating the dose around either radioactive liquid filled balloons or stents. A summary review of the various dose calculation methods are presented for the various delivery systems.

Catheter-based radioactive liquids: Radioactive liquid filled balloons have recently been used as a treatment delivery device. Currently, AAPM TG-60 does not recommend any dose calculation methods for liquid filled balloons. However, Monte Carlo and dose point kernel methods have been used for computing the dose distribution.

Radioactive Stents: At this time, dose calculation formalisms similar to TG-43 have not been proposed for use with radioactive stents because of the complex stent geometry. Investigators have used Monte Carlo and the dose point kernel methods for calculating the dose distribution around different types of stent geometries. Li et al. used the Monte Carlo N-Particle Transport Code (MCNP) for computing the dose around a positron emitting V48 nitinol stent ([14]). In this study, the stent was modeled as an array of cylindrical struts. MCNP was used to calculate the dose distribution around a single cylindrical strut. The dose distribution for the stent was then obtained by summing the dose contributions from the individual struts making up the stent. Janicki et al. used the dose point kernel (DPK) to calculate the dose distribution for a beta-emitting P-32 stent using the cylindrical wire mesh geometry for the Palmaz-Schatz™ stent ([15]).. An analytical dose function was derived using the known initial activity and distance of the calculation point to the center of the stent. The DPK function was numerically integrated using the geometry of the Palmaz-Schatz™ stent. The dose distribution generated by the beta particles was computed at distances ranging from 0.1 to 2 mm exterior to the stent surface.

External beam: Dose calculation methods for external beam have been used in radiation oncology for the past forty years. Over this time, sophisticated treatment planning systems have developed for predicting the dose distribution in a highly interactive and visual fashion. New delivery methods such as intensity modulated radiation therapy (IMRT) and gating technology could provide a method for delivering small field radiation to the site of the angioplasty.

Catheter-based seeds and wires: Sealed sources typically use either a dose point kernel method or a semi-empirical formalism with tabulated dosimetry parameters. The early work of dose calculation methods for sealed sources use the point source functions. Loevinger's point dose kernel was used for calculating the dose distribution from a P-32 wire ([16]). The dose for the point source is integrated for a line source. In addition, corrections must be applied for source encapsulation since most point source functions assume a unit density medium.

Another method that is familiar to medical physicists is the AAPM TG-43 protocol for calculating the dose distribution from interstitial sources. AAPM TG-60 recommends the use of the TG-43 dose calculation formalism for catheter-based systems using both gamma-emitting and beta-emitting sources (AAPM TG-43). The TG-43 method uses tabulated dose distribution data which is collected via dose measurements or Monte Carlo modeling techniques. These measurements are used to develop various tables based on the position and orientation of the source to the point of calculation. A dose calculation formula based on these tables is used for calculating the dose distribution around the source. Thus, the methods used to develop the dosimetry tables are very important and should be determined and validated for each delivery system. AAPM TG-60 recommends the source strength of gamma-emitting sources be specified in terms of its air kerma strength and be traceable to a NIST standard. A reference distance of 2 mm is also recommended for the reporting of the radial dose function. For beta-emitting sources, AAPM TG-60 recommends the dose at 2 mm in water be used as the reference point and substituted for the air kerma strength. A method developed by Soares at al. for calibrating beta sources is described in TG-60 ([17]).

Example of Validating Dose Calculation with Measurements: An example of the dose calculation and measured data is briefly described to illustrate both the accuracy and usefullness of the dose calculation software. This study focused on 1) calculating dose distributions for a Sr/Y-90 catheter-based system using the AAPM-Task Group 43 (TG43) dosimetry protocol, and 2) comparing the calculated dose distributions with measured data in a water-equivalent medium (A150 plastic). Measurements were made with radiochromic film in A150 plastic of a single Sr/Y-90 seed for constructing tables of data to determine the dose rate at an arbitrary point in A150 plastic. The absorbed dose-rate from a single seed to A150 plastic at a depth of 1.98 mm was determined to be 45 ± 6.8 mGy/s using an extrapolation chamber. A dose calculation model was developed for computing the dose distributions at any 3-D point in A150 plastic from any number of seeds using the AAPM TG43 formalism. Radiochromic films were exposed at different depths in A150 plastic, and digitized using a commercial CCD camera system. A

calibration curve was generated from a Sr/Y-90 ophthalmic applicator for converting optical density to absolute dose.

Isodose curves, dose profiles and depth-dose curves were produced for comparing measured and calculated data from both a single seed and a linear array of nine seeds (referred to as a source train). Figure 1 illustrates the agreement between the calculated and measured data at a depth of 1.98 mm in A150 for the radial dose profile. At distances greater than 0.8 mm to the source, the agreement was between the calculated and measured dose distributions was acceptable and within the uncertainty of the measured dose. Differences were observed between the calculated and measured dose data close to the source.

This type of dose calculation engine can be a useful foundation for treatment planning. Other types of delivery devices and sources can be modeled using a similar approach.

4. Special Considerations affecting Delivered Dose

Most dose prescription has assumed a linear source, centered in the vessel and a homogeneous, water equivalent absorbing media. In this section, situations are examined which differ from these assumptions that may potentially alter the dose delivered to the vessel wall.

Radius of curvature: Most stenotic segments treated with vascular brachytherapy are relatively short and the effect of curvature on the dose prescription and dosimetry has been generally discounted. Cases of marked curvature of the vessel (hinge angle of $< 45°$ at the stenotic site) were excluded from enrollment in certain clinical trials. Fox and Xu have reviewed the effects of the dose distribution from curved sources ([16,18]). Fox et al. investigated the radius of curvature effect on a ^{90}Sr/Y source train. A dose calculation model was developed for calculating the dose distributions using the AAPM TG-43 formalism. Xu et al. used Loevinger's method of point source functions to compute the dose distributions for a curved ^{32}P wire. Table 1 compares the effects of increasing curvature on the dose distribution for both an encapsulated ^{90}Sr/Y source train and a ^{32}P wire. As can be seen even marked curvatures of the source train did not result in more than a 20% increase in dose to points on the inner aspect of the curvature. These studies illustrate that hot and cold spots can result in a curved dose distribution for beta-emitting sources.

Long treatment length: Most coronary brachytherapy trials have been carried out using encapsulated seeds or wires of fixed length. On occasion the interventional cardiologist may encounter a long lesion or by intervention create a treated segment which exceeds the length of the source/source train. There are two methods for creating a longer treatment length: 1) use of a single source which is sequentially stepped to create the desired length and 2) manually aligning the source train in a sequential fashion. The first method can be accomplished with a remote afterloader device which requires a very accurate stepping motor. Most coronary systems have not employed this technology because of the length of time required to plan and treat the patient. Fox et al. investigated manually positioning the source trains adjacent to one another and the effect

of misalignment on the dosimetry at the junction of the two source trains.([19]) Two source trains of ^{90}Sr/Y (each train 23 mm length) were used in this model. A dose calculation model based on the AAPM TG-43 formalism was used for simulating the dose distributions. A dose enhancement factor (DEF) was calculated as the ratio of the dose at 2 mm between the two source trains for a source train misalignment to a perfect alignment. For perfect alignment, the DEF was unity. For various degrees of misalignment, the DEF varied from 0.47 for a 2 mm gap to 1.53 for a 2 mm overlap. Thus, when treating a stenotic segment longer than the treatment delivery device, precise (<1mm) colinear positioning of adjacent source trains may be necessary to ensure a smooth dose at the junction.

Attenuation by metallic stents: Significant dose perturbations in the dose distributions can occur from the presence of stent wires with a beta or gamma emitting catheter based system. The dose perturbation is more significant for beta sources than gamma sources due to the finite range of the beta particles and is caused by the greater scatter and absorption of beta than gamma particles. Several investigators have studied the effects of stents on the dose distribution for beta emitting sources ([20,21]). Amols investigated the effects of stenting with a Re-188 liquid filled balloon. The average dose rate was reduced for up to 14% for some stents with the severest inhomogeneities occurring near the stent surface. Beyond 0.5 mm from the stent surface, the dose distribution was similar to the unstented dose distribution.

Fox et al. examined the dose distribution effects of stents using a beta emitting (^{90}Sr/Y) catheter based system. The effect of a variety of stents (composed of stainless steel, tantulum, and nitanol) on the underlying dose distribution was examined by placing 6 thicknesses of radiochromic film underneath the expanded stent. Films were captured with a commercial CCD. To assess the degree of attenuation the relative dose/pixel along the long axis of the source train was plotted. Figure 2 represents relative dose versus distance along the long axis of the source train with and without a stent. The shadowing caused by the stent resulted in localized reductions of measured dose of up to 20% with tantulum stents. This effect becomes less signficant the further one is away from the stent. It should be pointed out that most metallic stents when expanded do not encompass more than 15% of the vessel surface. Similar perturbations in vessel wall dosimetry have been seen when accounting for the presence of calcifications in the vessel wall.

External beam target localization: In vascular radiotherapy, there has been some discussion of the use of external beam. One of the technical problems associated with external beam vascular radiotherapy is localizing and immobilizing the target volume for treatment. With new linear accelerator features, immobilization is not needed if gating technology is used. In layman's terms, gating technology simply allows the treatment beam to be turned on when artery is in the treatment field and turned off when the artery is outside the field. This technology may use the cardiac and respiratory cycles of the patient to pulse the beam on and off. Even with gating technology, the target must still be localized for both simulation and treatment. The use of new electronic portal imaging devices combined with metallic external/internal landmarks may provide a repeatable

procedure for target localization. In any event, the use of external beam will require an accurate and reproducible method for target localization.

Symmetrical Stent Deployment: In the previous section, the dose calculation methods presented for radioactive stents assumed that the stent was uniformly deployed in the artery. However, it is possible and common for the stent is to be non-uniformly deployed in the artery. If this happens, the dose distribution will even less uniformly distributed to the arterial wall.

Source Centering: Most of the treatment devices employed in the preclinical evaluation of vascular radiotherapy and many of the devices empoyed in current clinical studies have not involved the use of systems to center the source within the lumen. The dose to the vessel lumen may vary considerably as a result of that. This depends upon the type of source with the magnitude of the effect being less for more penetrating gamma sources. Centering the source within the lumen does not necessarily center the source within the vessel wall but is a reasonable first approximation.([22])

5. Dose Prescription

In prescribing radiation therapy for any purpose one needs to consider what the target tissue is and ensure that the desired dose is delivered to this target tissue. At this point in time the target tissue for vascular radiotherapy has not been conclusively established. Thus, prescription of radiation, in the early trials of ICRT, has been done in three distinctly different ways. In some trials, radiation has been prescribed at a fixed distance from the center of the source with the dose or distance being adjusted depending upon the reference vessel diameter. In other studies employing a balloon-centering device, the radiation has been prescribed at the balloon-lumen interface or at some depth from this structure. In addition, two trials have been completed where the investigators attempted to limit the maximum dose delivered to the media based on calculations of the delivered dose to a single near point in the treatment volume. However, none of these methods address whether the prescribed treatment will deliver the desired dose to the entire vessel wall. A goal of intravascular brachytherapy treatment planning is to enable the clinician to make a rapid, pre-treatment evaluation of the radiation dose delivered to the target structure and surrounding tissue and determine whether it is optimal.

Confusion regarding the actual dose delivered has resulted from the various prescription points employed. For example in preclinical studies using Ir-192, Wiederman found benefit only with doses of 15 Gy and above whereas Waksman, using the same source, found benefit with doses of 3.5 to 14 Gy with both authors using Ir-192. In looking at the details of their dose prescription the Emory group used the sources end-to-end without spacing and prescribed the dose at 2 mm. (the adventitial surface of the artery) whereas Wiederman used a 1 mm spacing between sources and prescribed the dose at 1.5 mm. In fact the 14 Gy prescribed by Waksman at 2 mm is the same as 20 Gy prescribed by Wiederman at 1.5 mm. Thus some but not all of the discrepancy between their results can be accounted for by examining the doses actually received by the target tissues.

TG-60 has recommended that for coronary applications each investigator report the dose delivered at 2 mm depth to allow comparisons to be made from one study to the

next. For larger peripheral vessels the task group recommends that the prescription point be determined by dividing the lumen diameter by 2 and adding 2 mm. Modification of the prescribed dose (or prescription point) for intracoronary catheter based techniques may need to be made on the basis of the size of the lumen and the presence of a stent or calcifications for low energy x-ray or beta emitting sources (see section 4).

A number of researchers feel that the target cell in the restenotic process originates in the adventitia of the artery. Prescribing dose to this point, this would require the use of Intravascular Ultrasound or IVUS to establish the distance from the source to the prescription point. The SCRIPPS Trial utilized IVUS to try to ensure that no portion of the vessel wall received what the authors felt might be an excessive dose (>30 Gy/single fraction) with this non-centered system. These investigators measured maximum and minimum distances from the ultrasound catheter to the leading edge of the media and prescribed 8 Gy to the maximum distance as long as 30 Gy to the minimum distance would not be exceeded. These authors have shown good efficacy and safety with this program suggesting that incorporation of IVUS may be useful in prescription of treatment. If the target cell for the therapy lies close to the vessel lumen on-line Quantitative Coronary Angiography may provide similarly beneficial information. TG-60 has recommended that in the initial feasibility studies of vascular radiotherapy that a number of IVUS images be taken through the treated area so that doses received by various parts of the vessel wall may be related to outcome (success or complications).

Most stent therapy has been prescribed based on the activity of the radioactive stent with only rudimentary evaluation of the dose delivered to the target tissues. Because the dose delivered is variable depending on the degree of expansion and the geometric structure of the stent, it may be impossible to know in advance exactly what the absorbed dose will be in the target tissues. No recommendations have been established for the prescription point for external beam techniques but this is less likely to be a concern because of the homogeneity of the dose throughout the treatment volume.

6. Dose Evaluation and Reporting

These sections discus the potential application of treatment planning to the field of vascular brachytherapy. Currently, the field of vascular brachytherapy uses treatment delivery devices in which the need for sophisticated treatment planning methods has not been established. In this section, a brief overview of basic applications for treatment planning are presented and based on work at Emory University over the past two years. Our institution has developed a real-time, three-dimensional (3-D) treatment planning system (*iPlan*™) for intravascular brachytherapy using intravascular ultrasound (IVUS) data. This systems allows the clinician to prospectively plan and evaluate the treatment delivered to the vessel wall using spatial dose distributions, dose volume histograms and figures of merit. The system allows various source delivery devices such as non-centered or lumen-centered source trains with ^{90}Sr/Y, ^{192}Ir and ^{125}I seeds.

Spatial Dose Evaluation: In typical radiation therapy planning systems, the patient anatomical data is obtained from computed tomography (CT) images. However, in vascular brachytherapy, CT images will not provide the detailed anatomical data of the arterial wall. Instead the use of intravascular ultrasound (IVUS) can been used to obtain

an anatomical map of the artery. IVUS images can be obtained from an automated pullback mechanism. In addition, the use of quantitative angiography (QCA) can be used for obtaining anatomical data on the patient; however, this type of imaging is limited to typically two orthogonal planes and may not provide accurate assessment of the arterial dimensions.

Quantitative Dose Evaluation: In addition to spatial dose evaluation, the use of quantitative dose evaluation methods such as dose volume histograms (DVH's) and dose surface histograms (DSH's) will provide a snapshot view of the dose-volume relationship for a particular treated segment. Figures 6 provides a representative illustration from *iPlan*™ which reflect dose volume histogram evaluation.

Treatment Planning Example: The use of a treatment planning system in vascular radiotherapy would provide the clinician with an objective software tool for prescribing, evaluating and reporting the dose given to a patient. At the same time it would provide a means of documenting the treatment given. At the current time, there is much debate on the necessity of a treatment planning system for vascular radiotherapy. At Emory University, a 3-D treatment planning system has been developed over the past two years and used for vascular radiation treatment delivery. The system (*iPlan*™) has been used to retrospectively evaluate individual patient treatments from clinical trials using IVUS data with a beta emitting delivery system. Using Figure 6 as an example, it illustrates the desired prescription dose rate of 14 cGy/s by the vertical line. The external elastic lamina (EEL) DVH is shown as a solid line, and the lumen DSH is shown as a dashed line. From the DVH, one can assess that only 25% of the EEL volume and 50% of the lumen surface receive the prescription dose rate of 14 cGy/s.

The use of treatment planning system may provide the clinician with a tool to further customize the radiation dose for individual patient treatments. This type of planning process may provide valuable information to the clinician before treatment and allow the customization of the treatment plan. It also may allow the clinician an opportunity to retrospectively evaluate the influence of dose on the success or side effects of the treatment. The presentation will present results from *iPlan*™ used in retrospective analysis of patient data in early vascular trials.

7. Conclusions

The role of therapy is to preserve an adequate lumen following coronary angioplasty. Furthermore, treatment should be planned such as to minimize any damage to the vessel from the treatment. In general the assessment of the prevention of restenosis is made at 6 months whereas late effects may result many years following this event. Although increasing inhibition of neointimal growth may be seen with increasing doses of radiation it is important to use the minimum effective dose until the late effects of intravascular brachytherapy are better understood. Clearly dosing in vascular radiotherapy is a complex issue and is critically important to the outcome. It is incumbent on the early investigators in this field to accumulate as much information as possible on the dose delivered to various parts of the vessel wall.

Table 1. Comparison of inner and outer dose rates for an increasing radius of curvature using both a Sr/Y-90 and P-32 line source.

Bending Angle (degrees)	**^{90}Sr/Y Outer Dose Rate**	**^{90}Sr/Y Inner Dose Rate**	**^{32}P Inner Dose Rate**	**^{32}P Outer Dose Rate**
0	1	1	1	1
30	0.98	1.02	0.9801	1.0295
45	0.97	1.03	0.9650	1.0638
60	0.96	1.04	0.9547	1.0755
90	0.94	1.06	0.9327	1.0865
135	0.93	1.11	0.8902	1.1942
180	0.91	1.17	N/A	N/A

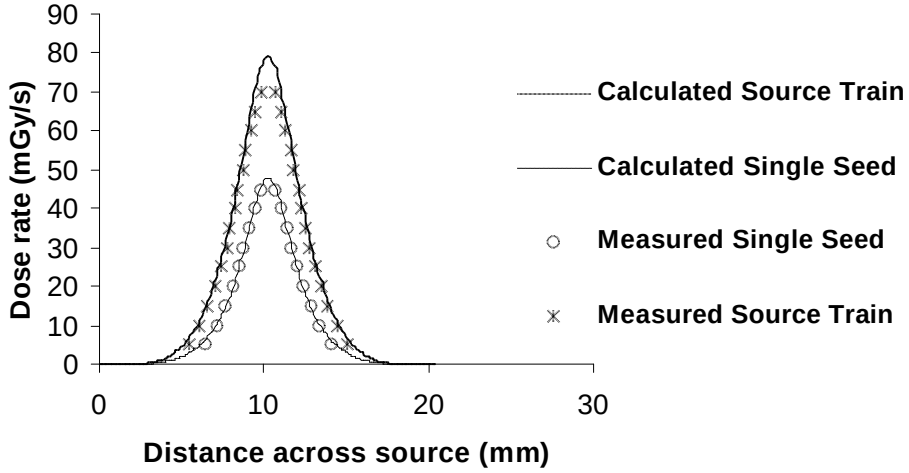

Figure 1. The agreement between the calculated and measured data at a depth of 1.98 mm in A150 for the radial dose profile is shown in graph A. The measured data is shown as a series of points and the calculated data is shown as a solid line.

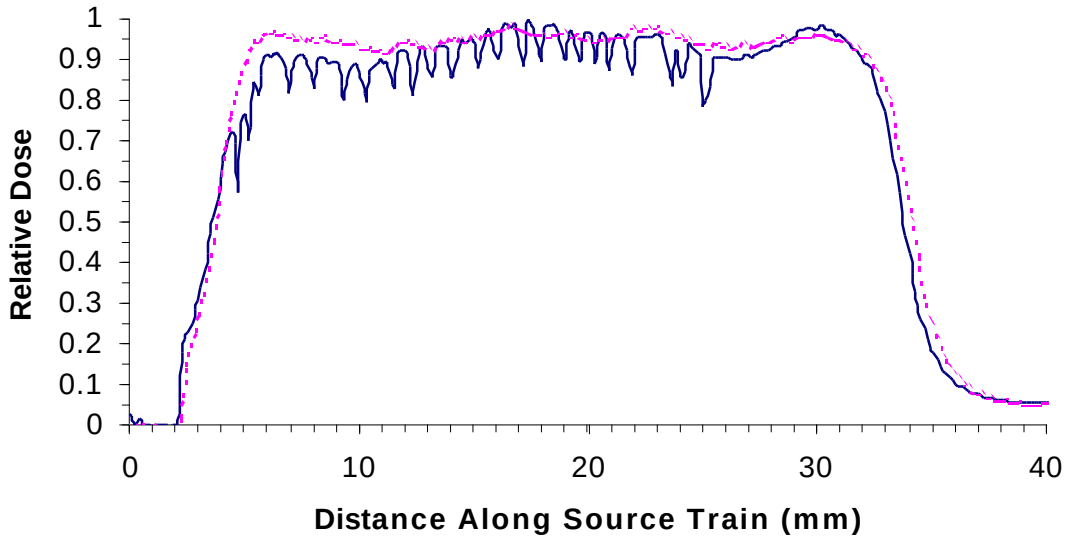

Figure 2. The relative dose versus distance along the long axis of the source train with (solid line) and without (dashed line) a stent is shown.

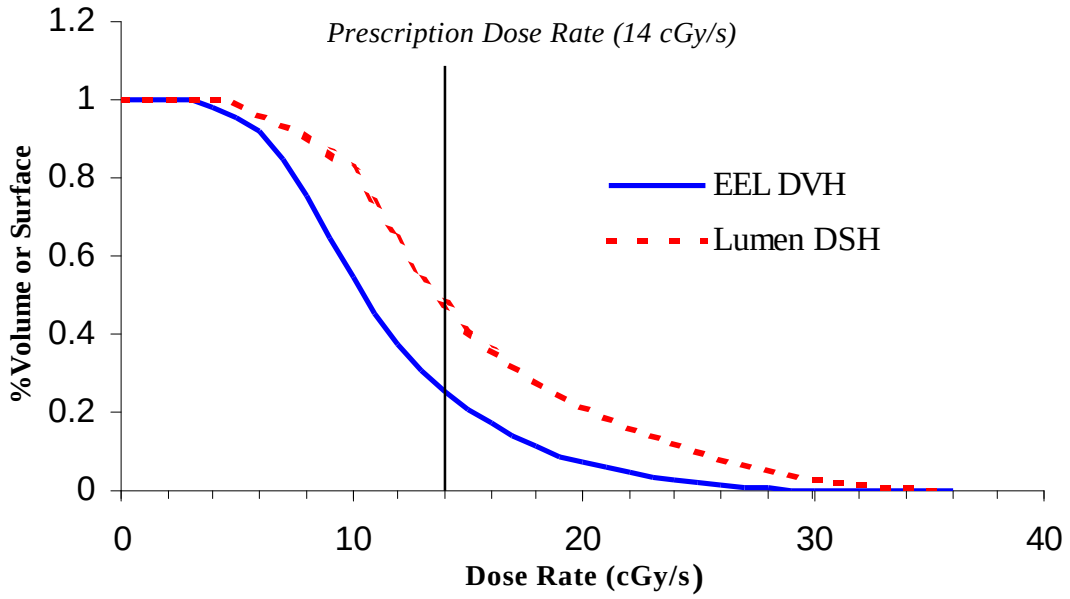

Figure 3. Quantitative dose evaluation using *iPlan*™ is shown with a DVH for the external elastic lamina (EEL) and a DSH for the lumen surface. The EEL DVH is shown as a solid line and the lumen DSH is shown as a dashed line.

References:

1. Waksman R, Robinson KA, Crocker IR, Gravanis MB, Cipolla GD, King SB III; Endovascular low dose irradiation inhibits neointima formation after coronary artery balloon injury in swine: a possible role for radiation therapy in restenosis prevention. *Circulation* 1995; 91: 1553-1539
2. Waksman R, Robinson K, Crocker I, Gravanis M, Palmer S, Wang C, Cipolla G, King, III S. Intracoronary Radiation Prior to Stent Implantation Inhibits Neointima Formation in Stented Porcine Coronary Arteries. *Circulation* 1995; 92:1383-1386
3. Waksman R, Robinson K, Crocker I, Wang C, Gravanis M, Cipolla G, Hillstead R, King, III S. Intracoronary Low Dose β-Irradiation Inhibits Neointima Formation After Coronary Artery Balloon Injury in the Swine Restenosis Model. *Circulation* 1995; 92: 3025-3031
4. Wiedermann JG, Marboe C, Amols H , Schwartz A, and Weinberger J. Intracoronary Irradiation Markedly reduces Neointimal Proliferation after Balloon Angioplasty in Swine: Persistent Benefit at 6-Month Follow-Up *J Am Coll Cardiol* 1995; 25: 1451-1456
5. Wiedermann JG, Marboe C, Schwartz A, Amols H, Weinberger J. Intracoronary Irradiation reduces restenosis after balloon angioplasty in a Porcine Model *J Am Coll Cardiol* 1994; 23: 1491-1498.
6. Weinberger J, Amols H, Ennis R, Schwartz A, Wiedermann J and Marboe C. Intracoronary irradiation: dose response for the prevention of restenosis in swine. International Journal of Radiation Oncology, Biology, Physics 1996; 36(4):767-75
7. Verin V, Popowski Y, Urban P, Belenger J, Redard M, Costa M, Widmer MC, Rouzaud M, Nouet P, Grob E, Schwager M, Kurtz J, Rutishauser W. Intra-arterial Beta Irradiation Prevents Neointimal Hyperplasia in a Hypercholesterolemic Rabbit Restenosis Model *Circulation* 1995; 92: 2284-2290
8. Mazur W, Ali MN, Khan M, Dabaghi S, DeFelice C, Paradis P, Butler E, Wright A, Fajardo L, French B, Raizner A. High dose rate intracoronary radiation for inhibition of neointimal formation in the stented and balloon-injured porcine models of restenosis: angiographic, morphometric, and histopathologic analyses. International Journal of Radiation Oncology, Biology, Physics 1996; 36(4):777-88
9. Hehrlein C, Gollan C, Donges K, Metz J, Riessen R, Fehsenfeld P, von Hodenberg E, Kubler W. Low-dose radioactive endovascular stents prevent smooth muscle cell proliferation and neointimal hyperplasia in rabbits. Circulation 1995; 92(6):1570-5
10. Carter A, Laird J, Bailey L, Hoopes T, Farb A, Fischell D, Fischell R, Fischell T, and Virmani R. Effects of endovascular radiation from a beta-particle-emitting stent in a porcine coronary restenosis model. A dose-response study Circulation 1996; 94(10):2364-8

11. Laird J, Carter A, Kufs W, Hoopes T, Farb A. Nott S, Fischell R, Fischell D, Virmani R, and Fischell T. Inhibition of neointimal proliferation with low-dose irradiation from a beta-particle-emitting stent. Circulation 1996; 93(3):529-36

12. Waksman R. Clinical Trials in Radiation Therapy for Restenosis: Past, Present and Future. Vascular Radiotherapy Monitor. 1998; 10-18

13. Soares, C. "Radiation: The basics". Vascular Radiotherapy Monitor, Vol. 1, number 1, 1998.

14. Li A, Eigler N, Litvack F and Whiting J. Characterization of a positron emitting V48 nitinol stent for intracoronary brachytherapy. Medical Physics 1998. 25(1):20-8,

15. Janicki C, Duggan D, Coffey C, Fischell D, and Fischell T. Radiation Dose From A Phosphorous-32 Impregnated Wire Mesh Vascular Stent. Medical Physics. 24(3):437-445, 1997

16. Xu Z Reinstein L, Yang G, Pai S, Gluckman G and Almond P. The Investigation Of P-32 Wire For Catheter-Based Endovascular Irradiation. Medical Physics. 24(11):1788-1792, 1997

17. Soares C, Halpern D, Wang CK. Calibration and characterization of beta-particle sources for intravascular brachytherapy. Medical Physics. 25(3):339-46, 1998

18. Fox T, Soares C, King SB III, Robinson K, Davis L, Crocker I: Effect of curvature on dosimetry from a beta-emitting source train. Advances in Cardiovascular Radiation Therapy II. March 8-10, 1998, Washington, D.C.

19. Fox T, Soares C. King SB III, Robinson K, Davis L, Crocker I. Co-linear alignment of a beta-emitting radiation source train: Dose effect of misalignment at the junction. Advances in Cardiovascular Radiation Therapy II. March 8-10, 1998, Washington, D.C.

20. Fox T, Lobdell J, Robinson K, King SBIII, Davis L and Crocker, I. Attenuation of dose from a ^{90}-Sr/Y Line Source by a Stainless-Steel Stent. Second Annual Symposium on Radiotherapy to Reduce Restenosis. LaJolla, Ca. 1/16/-1/17/98.

21. Amols H. Dose Distributions pre-and post-Stenting for Beta sources. Advances in Cardiovascular Radiation Therapy II., Washington DC, 1998

22. Marijnissen J, Levendag P, Coen V, Visser A, Carlier S, Ligthart J and Serruys P. Gamma and Beta Source Dosimetry and Dose Volume Histograms from Intravascular Ultrasound (IVUS). Advances in Cardiovascular Radiation Therapy II., Washington DC, 1998