This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

DRAFT Version 1.3a

Intravascular Brachytherapy - Guidance for Data to be Submitted to the Food and Drug Administration in Support of Investigational Device Exemption (IDE) Applications

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U.S. Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

Draft Guidance for Intravascular Brachytherapy IDE Applications

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Introduction

The Food and Drug Administration (FDA) considers the use of radiation in the coronary and/or peripheral vasculature (intravascular brachytherapy) for the prevention of restenosis an unproven therapy with the potential for significant risk to patients. Legal and ethical considerations require that U.S. patients be studied under an investigational device exemption (IDE) application.

The purpose of this guidance is to provide a general framework for the format and content of an IDE application for intravascular brachytherapy. IDEs for external beam irradiation of the vasculature can be addressed by utilizing the concepts included in this guidance, where applicable. The guidance is tailored towards sponsor/investigator IDEs. If you have a well designed study and your protocol has been reviewed by an Investigational Review Board (IRB), you may have already met many of the IDE requirements.

If you can readily provide the information outlined below, you may submit an IDE directly. However, if you are uncertain about the adequacy of your data and/or protocol, you may submit a pre-IDE. A pre-IDE is the mechanism whereby FDA can provide prompt, informal feedback regarding specific aspects of your application.

If you have questions regarding this Guidance, please call one of the contacts listed below at (301) 443-8243. Additional general information regarding investigational device exemption (IDE) applications may obtained from CDRH's Division of Small Manufacturer's Assistance by calling (800) 638-2041 or (301) 443-6597.

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Specific IDE Requirements

1. Identify yourself, your center and other centers involved.

2. Identify the radioactive isotope and the method which will be used to deliver the radiation. Also, specify the manufacturer(s) of the source and delivery system.

3. Provide a **Report of Prior Investigations** (bench, animal and clinical) conducted with the system you intend to use in your investigation.

   a. Bench Testing

   Much of the bench testing may have already been conducted by the manufacturer. A list of the types of bench testing which FDA believes is appropriate to qualify brachytherapy systems is provided in Attachment A. Clinical investigators should forward this list to the manufacturer. The manufacturer may provide this information directly to the investigator for inclusion in the IDE application. Alternatively, the manufacturer may provide the investigator a letter which allows the investigator to reference appropriate files within the Agency where this bench testing is contained. This letter should clearly specify the file numbers (or master file) and pages where these test data can be found and should be included in the IDE application.

   b. Animal Testing

   Describe any animal tests conducted using the radiation source and delivery system you intend to use in your investigation. Work done by others may be referenced; however differences in components and/or experimental methodologies should be noted and an explanation provided as to how such data are applicable to your study. (Attachment B contains a comprehensive intravascular brachytherapy bibliography). Also, state whether the animal testing was done in compliance with Good Laboratory Practices (GLPs). These regulations are contained in 21 CFR part 58 *Good Laboratory Practices for Nonclinical Laboratory Studies* and may be obtained from DSMA.

   c. Clinical Experience

   Provide all clinical data available using the radiation source and delivery system you intend to use in your investigation. Similar to the animal test results, work done by others may be referenced but a justification is needed for how this data is applicable if the radiation source, delivery system and/or methods used were different from those proposed in your study.

4. Provide a copy of your **Investigational Plan**. Included in your plan should be the following:

   a. **Purpose** should clearly define:
      - Name and intended use of the device
      - Objectives of the investigation
      - Duration of the investigation

b. **Protocol and Case Report Forms (CRF)** - The protocol should provide an adequate description of the methodology involved, including:

- a list of the inclusion/exclusion criteria
- a statement of the study objective (hypothesis)
- identification of a control group
- calculation of sample size
- description of patient screening and recruitment procedures
- description of treatment assignment (randomization methods)
- a list of outcome variables or endpoints
- definitions of success, failure and complications
- a description of all baseline and follow-up assessments (NOTE: At present FDA believes patients undergoing this therapy should undergo, at a minimum, angiographic follow-up at 6 months and clinical follow-up at 12 and 24 months)
- blank copies of the CRFs.
- identification of the professional disciplines of those involved in the study, e.g., cardiologists, interventional radiologists, radiation oncologists, health physicists, medical (radiation) physicists, etc.
- specification of the lesions which will be irradiated, i.e., *de novo*, restenotic, and/or stented
- clarification regarding whether radiation is delivered during the interventional procedure and in the same room. Also describe whether transportation of the patient to a separate facility for radiation is required.

c. **A risk analysis** should support the finding of an adequate benefit to risk ratio.

- Describe and analyze the patient risks, especially problems already encountered. Included in your description should be a discussion concerning the length of time the source will be in place in the vessel and the adequacy of blood flow during this time. Also an approximation of the fluoroscopy time required for the procedure and the potential for fluoroscopy burns should be described.
- Describe how the risks will be minimized
- Justify the risks
- Describe the patient population (age, sex, medical condition)

d. **Description of the device**

- List each component of the source/delivery system.
- State the principal and mode of operation, including a description of how the source is centered, if applicable.
- If not centered, address the consequences to dose distribution within the lesion and vessel.
- Specify the therapeutic dose(s) which will be delivered to the lesion and provide a rationale for the choice of this dose(s).
- Specify the dose prescription point(s) in the lesion and the dose expected to be delivered to the closest point in the intima and furthest point in the adventitia. Discuss this dose(s) in light of the potential for tissue damage, i.e., necrosis, aneurysms, etc.
- Specify the source strength, delivered dose, and distance for each dose specification.
- Describe how the therapeutic dose to the lesion and the spatial distribution of this dose are estimated.
- Describe how this dose and dose distribution are validated.
- Describe quality assurance (QA) and radiation safety procedures which will be followed at your center, e.g., NRC or state license requirements for reactor-produced isotopes. Otherwise provide similar procedures for non-NRC sources, as appropriate.
- Specify the applicability of any national, state and/or local regulations regarding the use of radioactive substances, and your compliance with these regulations. (See Attachment C)

e. **Monitoring Procedures**

- Name and address of the study monitor
- Description of the monitoring procedure

5. **Manufacturing Information**

Provide information regarding the manufacture, processing, packaging, transport and storage of all components which will be used in your study. The manufacturer can provide this information to you directly for inclusion in the IDE application. Alternatively, a letter granting Agency access to this information may be provided.

6. **Investigator Agreement**

a. a sample of the investigator's agreement

b. name, address, and fax number of all investigators who have signed the investigator agreement

c. certification that no investigators will be included in the study until the investigator agreement is signed

d. specification of the cardiologist, interventional radiologist, radiation oncologist, medical (radiation) physicist, and others as appropriate.

7. **Institutional Review Board (IRB) Information and Informed Consent Form**

   a. Provide the name and address of each IRB chairperson.

   b. Include a copy of the informed consent form (see Attachment D. Informed Consent Required Elements).

   c. Describe the action taken by the IRB, i.e., study approval.

   d. If this is a multicenter study, specify how many IRBs have approved and how many are currently reviewing the study protocol and informed consent.

8. **Sales Information**

   a. Is the device/treatment to be sold? (yes or no)

   b. If yes, how much will be charged to the patient?

   c. Explain why sale does not amount to commercialization.

9. **Other Information**

   a. **Labeling** - Provide copies of package labels and Instructions for Use that accompany the device(s) that you will be using.

   b. Submit an environmental assessment as described 21 CFR 25.31(a), or claim a categorical exclusion from this requirement by stating to us that "devices shipped under the Investigational Device Exemption are intended to be used for clinical studies in which waste will be controlled or the amount of waste expected to enter the environment may reasonable be expected to be nontoxic" as provided for in 21 CFR 25.24(e)(7).

c. Verify your understanding of the responsibilities of a sponsor of an investigational device

Attachment A. Bench Testing

1. Characterization of Radiation source
   - radiation type (alpha, beta, gamma, x-ray)
   - radiation half-life, average and maximum energy (MeV) as appropriate
   - activity of the source (curie or Bq)
   - source configuration (encapsulation, plating, etc.)
   - source uniformity (linear activity)
   - dose distribution map (iso-dose curves providing three-dimensional representation of the dose)
   - plot of absorbed dose rate vs. distance in a properly selected medium
   - algorithms used to calculate the dose, including attenuation by the medium in which the irradiation is performed
   - method of radiation source calibration, including accuracy and precision
   - a description of the software used to calculate doses and dose distribution (note that good software developing practices should be utilized as described in "Reviewers Guidance for Computer-Controlled Medical Devices Undergoing 510(k) Review").
   - a description of the testing done to ensure that the calculated dose distribution is validated

2. Biocompatibility of blood-contacting materials used in the delivery system (if applicable)

3. Mechanical Integrity of components used in the delivery system (if applicable)

4. Sterility of the source and delivery system

Attachment B. Intravascular Brachytherapy Bibliography

This document collects citations to the primary literature, abstracts, books, and other published and unpublished documents relevant to intravascular brachytherapy, particularly of the coronary arteries, collected by the CDRH Office of Device Evaluation (ODE). The first 49 were collected by Charles Coffey, Vanderbilt University Medical Center. Any citation marked with a *, is on file in the ODE (HFZ-450) offices, 9200 Corporate Boulevard, Rockville, MD 20850. Citations marked with a superscript [a] are abstracts only. Questions -- call John Stuhlmuller 301-443-8609, InterNet: JES@FDADR.CDRH.FDA.gov.

1. Fonkalsrud EW, Sanchez M, Zerubavel R, Mahoney A: Serial changes in .arterial structure following radiation therapy. Surgery Gynecology and Obstetrics 145: 395-400 (1977).

2. Clowes AW, Reidy MA, Clowes MM: Mechanisms of stenosis after arterial injury. Laboratory Investigation 49: 208-215 (1983).

3.* Rosen E, Goldberg K, Myrick K: Radiation survival properties of cultured vascular smooth muscle cells. Radiation Research 1984; 100: 182-91.

4. Austin GE, Ratliff NB, Hollman J, Tabei S, Phillips DF: Intimal proliferation of smooth muscle cells as an explanation for recurrent coronary artery stenosis after percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 6: 369-375 (1985).

5. Dunsmore LD, LoPonte MA, Dunsmore RA: Radiation-induced coronary artery disease. J Am Coll Cardiol 8: 239-244 (1986).

6. Ayers DC, Evarts CM, Parkinson JR: The prevention of heterotopic ossification in high risk patients by low dose radiation therapy after hip anthroplasty. J Bone Joint Surgery 68: 1423-1430 (1986).

7. McPherson DD, Armstrong M, Rose E, Kieso RA, Megan M, Hunt M, Hite P, Marcus ML, Kerber RE: High frequency epicardial echocardiography for coronary artery evaluation: in vitro and in vivo validation of arterial lumen and wall thickness measurements. J Am Coll Cardiol 8: 600-606 (1986).

8. Sylvester JE, Greenberc P, Selch MT: The use of postoperative irradiation for the prevention of heterotopic bone formation after total hip replacement. Int J Radiation Oncology Biol Phys 14: 471-476 (1988).

9. Kovalic JJ, Perez CA: Radiation therapy following keloidectomy: a 20 year experience. Int J Radiation Oncology Biol Phys 17: 77-80 (1989).

10. Gillette EL, Powers BE, McChesney SL, Park RD, Withrow SJ: Response of aorta and branch arteries to experimental intraoperative irradiation. Int J Radiation Oncology Biol Phys 17: 1247-1255 (1989).

11. Schwartz RS, Murphy JG. Edwards WD, Camrud AR, Vliesta MB, Holmes DR: Restenosis after balloon angioplasty: a practical proliferative model in porcine cornoary arteries. Circulation 82: 2190-2200 (1990).

12. Dawson JT. Theoretic considerations regarding low-dose radiation therapy for prevention of restenosis after angioplasty. Texas Heart Institute Journal 1991; 18:4-7.

13. St Goar FG, Pinto FJ, Alderman EL, Fitzgerald PJ, Stadius ML, Popp RL: Intravascular ultrasound imaging of angiographically normal coronary arteries: an in vivo comparison with quantitative angiography. J Am Coll Cardiol 18: 952-958 (1991).

14. Gellman J, Healey G, Qingsheng C, Tseientakis: The effect of very low dose irradiation on restenosis following. balloon angioplasty. a study in the atherosclerotic rabbit. Circulation 84: 46A-59A (abstract) (1991).

15. Hermans WRM, Rensing BJ, Strauss BK, Serruys PW: Prevention of restenosis after percutaneous transluminal coronary angioplasry (PTCA): the search for a "magic bullet." American Heart Journal 122: 171-187 (1991).

16. Fischell TA, Abbas MA, Kallman RF. Low-dose irradiation inhibits clonal proliferation of smooth muscles: a new approach to restenosis. Arterioscler Thromb 1991; 11: 1435.

17.* Schwartz RS, Koval TM, Edwards WD, Camrud.AR, Bailey KR, Browne K, Vlietstra RE, Holmse DR: Effect of external beam irradiation on neointimal hyperplasia after experimental coronary artery injury. J Am Coll Cardiol 1992; 19: 1106-13. d [113.57]

18. St Goar FG, Pinto FJ, Alderman PJ, Fitzgerald PJ, Stinson EB, Billingharn ME, Popp RL: Detection of coronary atherosclerosis in young adult hearts using intravascular ultrasound. Circulation 86: 756-763 (1992).

19. Koras SP, Gravanis NM, Santoian ED, Robinson KA, Anderberg KA, King SB: Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. J Am Coll Cardiol 20: 467-474 (1992).

20. Pellegrini VD, Konski AA, Gastel JA, et al: Prevention of heterotopic ossification with irradiation after total hip anthroplasty. J Bone Joint Surgery 74: 186-200 (1992).

21. Wiedermann JG, Leavy J, Amols H, Homma S, DiTullio K, Sherman D, Apfelbaum K, Schwartz A, Weinberger J: Circulation 86: 1-188 (abstract) (1992).

22. Wilder RB, Buatt JK, Kittleson JM, Shimm DS, Hevari PM, Rogoff EE, Cassady JR: Pterygium treated with excision and post-opertative beta irradiation. Int J Radiation Oncology Biol Phys 23: 533-537(1992).

23. Abbas NA, Afshari NA, Stadius ML, Ferrioffi RS, Fischell TA: Effect of x-ray irradiation on neointimal proliferation following balloon angioplasty. Clinical Research 41-79 (abstract) (1993).

24. Shefer A, Eigler NL, Whiting JS, Litvack FIL Suppression of intimal proliferation after balloon angioplasty with local beta irradiation in rabbits. J Am Coll Cardiol 21: 185 (abstract) (1993).

25. Hehrlein C, Zimmerman M, Metz J, Felisenfeld P, von Hodenberg E: Radioactive coronary stent implantation inhibits neointimal proliferation in nonatherosclerotic rabbits. Circulation 88: 1-650 (abstract) (1993).

26. Escarmont A. Zimmerman S, Ainer A, *et al:* The treatment of 787 keloid scars by iridium 192 interstial irradiation after surgical excision. Int J Radiation Oncology Biol Phys 26: 245-251 (1993).

27. Parvani SB, Scott WP, Wells JW, Johnson DW, Chobe RJ, Kuruvilla A, Schoeppel S, Deshmukh A: Management of pterygium with surgery and radiation therapy. Int J Radiation Oncology Biol Phys 28: 101-103 (1994).

28.[a] Shimotakahara S; Mayberg MR Gamma irradiation inhibits neointimal hyperplasia in rats after arterial injury [see comments] Stroke 1994 Feb;25(2):424-8 Comment in: Stroke 1995 May;26(5):903-5

Abs: Folks from Otolaryngology Head and Neck Surgery at U Washington, Seattle, produced a standardized bilateral carotid artery injury in 37 rats and gave single dose of 750, 1500, or 2250 cGy (1cGy = 1 rad) gamma radiation to the right carotid artery at either 1 or 2 days after injury. Marked reductions in neointimal cross-sectional area were demonstrated in vessels subjected to 1500- and 2250-cGy radiation at both 1 and 2 days after injury. The effect for 750 cGy reached statistical significance only at 2 days after injury. Radiation dose (P = .0002), timing of radiation delivery (P = .003), and an interaction between timing and dose (P = .0278) were significantly associated with reduction in neointimal cross-sectional area. At 1500 cGy, delivery of radiation 1 day after injury inhibited neointimal hyperplasia more prominently than the same dose 2 days after injury; a dose-response relation was evident at 1 day.

29.* Bottcher HD, Schopohl B, Liermann D, Kollath J, Adamietz 1A. Endovascular irradiation-a new method to avoid recurrent stenosis after stent implantation in peripheral arteries: technique and preliminary results. Int J Radiation Oncology Biol Phys 1994; 29: 183-6.

30.* Fischell TA; Kharma BK; Fischell DR; Loges PG; Coffey CW 2nd; Duggan DM; Naftilan AJ: Low-dose, beta-particle emission from 'stent' wire results in complete, localized inhibition of smooth muscle cell proliferation [see comments] Circulation 1994 Dec;90(6):2956-63 Comment in: Circulation 1995 Sep 1;92(5):1353-4

Abs: Very low doses of beta-particle emission from a 32P-impregnated stent wire (activity levels as low as 0.006 microCi/cm of wire) completely inhibited the growth and migration of both rat and human SMCs within a range of 5.5 to 10.6 mm from the wire. Endothelial cells appeared to be much more radioresistant than SMCs. These data suggest that an intra-arterial stent impregnated with a low concentration of 32P may have a salutary effect on the restenosis process. Division of Cardiology, Vanderbilt, Nashville.

31.* Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J: Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model. J Am Coll Cardiol 1994; 23:1491-8. d [113.72]

32. Berner BM, Wright AE, Gram W, Butler B: Arterial brachytherapy. Medical Physics 21: 96 (abstract) (1994).

33. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J: Intracoronary irradiation.-minimal effective dose for prevention of restenosis in swine. Circulation 90: 1-142 (abstract) (1994).

34. Waksman R, Robinson KA, Crocker IR, Cipolla GD, King SB: Endovascular irradiation inhibits a restenosis-like response after balloon angioplasty of pig coronaries: dose-response relationship. Circulation 90 :1-142 (abstract) (1994).

35*. Mazur W, Ali NM, Dabaghi SF. Grinstead WC, Abulchalil J, Paradisc P, DeFelice CA, Schulz D, Berner B, Fajardo.LF, Brench BA, Raizner AE: High dose rate intracoronary radiation suppresses neointimal proliferation in the stented and ballooned model of porcine restenosis. Circulation 1994; 90: 1-652 (abstract).

36.* Liermann D, Bottcher HD, Kollath J, Schopohl B, Strassman G. Strecker P, Breddin KH: Prophylactic endovascular radiotherapy to prevent intimal hyperplasia after stent implantation in femoropopliteal arteries. Cardiovasc Intervent Radiol 1994; 17: 12-16.

37.* Wiedermann JG, Marboe C, Amols H, Schwarz A, Weinberger J: Intracoronary irradiation markedly reduces restenosis after balloon angioplasty in a porcine model: six month follow-up. Circulation 1994; 90: 1-652 (abstract).

38. Wiedermann JG, Leavy JA_ Amols H, Schwartz A, Homma S, Marboe C, Weinberger J: Effects of high-dose intracoronary irradiation on vasomotor function and smooth muscle histopathology. American J Physiology (Heart Circ. Physiology 36:) H125-HI32 (1994).

39. Gehman KE, Gaspar LE, Barnett R, et al: High dose rate endovascular irradiation: tolerance of normal tissues. Endocuritherapy/Hyperthermia Oncology 10:167-171 (1994).

40. Prestwich WV, Kennett TJ, Kus FW: The dose distribution produced by a P32-coated stent. Medical Physics 22: 313-320 (1995).

41. Popowski Y, Verin V, Papirov I, Notiet P, Rouzatid K, Grob E, Schwager K, Urban P, Rutishauser W, Kurtz. JM: High dose rate brachytherapy for prevention of restenosis after dosimetric tests of a new source presentation. Int J Radiation Oncology Biol Phys 33: 211-215 (1995).

42.* Sarac TP, Riggs PN, Williams JO, Feins RH, Baggs R, Rubin P, Green RM: The effects of low dose radiation on neointimal hyperplasia. J Vas Surg 1995; 22: 17-24.

43. Ly NC, Whitincy JS, DeFrance A, Elgler NI: A novel brachytherapy source for treatment of coronary artery restenosis. Medical Physics 22: 92 (abstract) (1995).

44. Wiedermann JG, Marboe C, Amols H, Schwartz A, Weinberger J: Intracoronary irradiation fails to reduce neointimal proliferation after oversized stenting in a porcine model. Circulation 92 (8): 146 (abstract) (1995).

45. Waksman R, Robinson KA, Crocker IR, Wang C, Gravanis B, Cipolla GD, Hillistead RA, King SB: Efficacy and safety of beta versus gamma radioisotopes for endovascular irradiation in prevention of intimal hyperplasia after balloon angioplasty in swine coronaries. Circulation 1995; 92(8): 146 (abstract)

46. Hehrlein C, Kaiser S, Kollum M, Kinscherf R, Fehsenfeld P: Effects of very low dose endovascular irradiation via an activated guide-wire on neointima formation after stent implantation. Circulation 92(8): 146 (abstract) (1995).

47.* Waksman R; Robinson KA; Crocker IR; Wang C; Gravanis MB; Cipolla GD; Hillstead RA; King SB 3rd: Intracoronary low-dose beta-irradiation inhibits neointima formation after coronary artery balloon injury in the swine restenosis model.Circulation 1995 Nov 15;92(10):3025-31. d [113.94]

Abs: Administration of endovascular beta-radiation to the site of coronary arterial overstretch balloon injury in pigs with 90Sr/Y in doses between 7 and 56 Gy showed evidence of inhibition of neointima formation. A dose-response relation was demonstrated, but no further inhibitory effect was seen beyond 28 Gy. Andreas Gruentzig Cardiovascular Center, Department of Medicine, Emory, Atlanta.

48. Teirstein PS, Massullo V, Jani S, Russo RJ, Schatz A, Steuterman S, Morris N, Tripuraneni P: Catheter-based radiation therapy to inhibit restenosis following coronary stenting. Circulation 92 (8): 543 (abstract) (1995).

49. Popowski Y, Verin V, Papirov I, Nouet P, Rouzaud M, Schwager M, Ing D , Urban P, Rutishauser W, Kurtz JM: Intra-arterial Y90 brachytherapy: preliminary dosimetric study using a specialty modified angioplasty balloon. Int J Radiation Oncology Biol Phys 33: 713-717 (1995).

50. Capek P, McLean GK, Berkowitz HD. Femoropopliteal angioplasty. Factors influencing long-term success. Circulation 1991;83(suppl 1):1-70-I-80.

51. Jeans WD, Armstrong S, Cole SEA, Horrocks M, Baird RN. Fate of patients undergoing transluminal angioplasty for lower-limb ischemia. Radiology 1990;177:559-64.

52. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology 1992;183:767-71.

53. Forrester A Fishbein M, Helfant R, Fagin J A paradigm for restenosis based on cell biology; clues for the development of new preventive therapies. J Am Coll Cardiol. 199 1; 1 7:758-69.

54. Ross R. Pathophysiology of atherosclerosis. In: Veith FJ, Hobson RW, Williams RA, Wilson SE, ed. Vascular Surgery. Second Edition ed. New York: McGraw Hill, 1994: 1 1.

55. Ferns GAA, Raines EW, Sprugel KH, Motani AS, Reidy MA. Inhibition of neointimal smooth muscle accumulation after angioplasty by an antibody to PDGF. Science 1991;253(5024):1129-32.

56.* Fischell TA, Kharma BK, Fischell DR, et al. Low-dose, β-particle emission from "stent" wire results in complete, localized inhibition of smooth muscle cell proliferation. Circulation 1994; 90: 2956-63. [113.117]

57. Schopohl B. Endovascular Radiation in peripheral vascular system. In: King SB, Waksman R, Crocker IR, ed. Discoveries in radiation for restenosis. Atlanta: , 1996: .

58. Abbas MA, Benitz WE, Fischell TA. Comparative effects of single and fractionated doses of irradiation upon smooth muscle cells in culture. Clinical Research 1992;40:43A.

59.* Waksman R, Robinson KA, Crocker IR, Gravanis MB, Clpolla GD, King SB. Endovascular low-dose irradiation inhibits neointimal formation after coronary artery balloon injury in the swine -- a possible role for radiation therapy in restenosis prevention. Circulation 1995;91:1533-9. d [113.65]

60. Teirstein PS. Endovascular radiation in human coronary arteries. In: King SB, Waksman R, Crocker IR, ed. Discoveries in radiation for restenosis. Atlanta, Georgia: , 1996: .

61. Waksman R. Endovascular radiation therapy for restenosis. 8th International Brachytherapy Conference. Nice: 1995

62. Fontenla DP, Deore SM, Beitler JJ High dose rate intravascular brachytherapy for coronary artery restenosis. Submitted to AAPM 1996;.

63. Veith FJ, Panetta TF, Wengerter KR, et al. Femoralpopliteal-tibial occlusive disease. In: Veith FJ, Hobson RW, Williams RA, Wilson SE, ed. Vascular Surgery: Principles and Practice. 2nd ed. New York: McGraw-Hill, Inc, 1994: 422.

64.* Werber J, Sood BM, Alfieri A, McCormick S, Vikram B. Tolerance of the Carotid Sheath Contents to Brachytherapy. Laryngoscope 1991;101:587-91.

65. Imparato AM, Kim GE, Davidson T, Crowley JG: Intermittent claudication: Its natural course. Surgery 1975;78:795.

66. Coran AG, Warren R. Arteriographic changes in. femoropopliteal arteriosclerosis obliterans: A five year follow-up study. N Eng J Med 1966; 274: 643.

67. Green RM. Annual Incidence of Infrainguinal Angioplasty at the University of Rochester School of Medicine and Dentistry. In: 1995:

68. Bandyk DF. Postoperative surveillance of infrainguinal bypass. Surg Clin North Am 1990;70:71-85.

69. Blair JF, Bandyk DF. Real-time color Doppler in arterial imaging. In: Yao JST, Pearce WH, ed. Technologies in Vascular Surgery. Philadelphia, PA: Saunders, 1991: 129-49.

70.* Lederman GS, Sheldon TA, Chaffey JT, Herman TS, Gelman RS, Coleman CN: Cardiac disease after mediasteinal irradiation for seminona. Cancer 1987; 60: 772-6.

71.* Kopelson G, Herwig KJ: The etiologies of coronary artery disease in cancer patients. Int J Radiation Oncology Biol Phys 1978; 4: 895-906.

72.* Applefield MW, Slawson RG, Spicer KM, Singleton RT, Wesley MN, Wiernik PH: Long term cardiovascular evaluation of patients with Hodgkin's Disease treated by thoracic mantle radiotherapy. Cancer Treat Rep 1982; 66: 1003-13.

73.* Prentice RTW: Myocardial infarction following radiation, Lancet 1965; August 21: 388. (letter)

74.* Gold H: Production of arteriosclerosis in the rat -- effect of x-ray and a high fat diet. Arch Pathol 1961; 71:268-73.

75.* Brosius FC, Waller BF, Roberts WC: Radiation heart disease -- analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. Am J Med 1981; 70: 519-30.

76.* Lamberts HB, de Boer WGRM: Contributions to the study of immediate and early X-ray reactions with regard to chemoprotection VII. X-ray-induced atheromatous lesions in the arterial wall of hypercholesteraemic rabbits. Int J Rad Biol ?1963; 6(4): 343-50.

77.* Stewart JR, Cohn KE, Fajardo LF, Hancock EW, Kaplan HS: Radiation-induced heart disease. Radiology 1967; 89: 302-10.

78.* Voivin JF, Hutchinson GB: Coronary heart disease mortality after irradiation for Hodgkin's Disease. Cancer 1982; 49: 2470-5.

79.* Annest LS, Anderson RP, Li W, Hafermann MD: Coronary artery disease following mediasteinal radiation therapy. J Thorac Cardiovasc Surg 1983; 85: 257-63.

80.* Lindsay S, Kohn HI, Dakin RL, Jew J: Aortic arteriosclerosis in the dog after localized aortic x-irradiation. Circulation Research 1962; 10: 51-60.

81.* Soares CG, McLaughlin WL: Measurement of radial dose distributions around small beta particle emitters using high resolution radiochromic foil dosimetry. Radiat Prot Dosim 1993; 47: 367-72. d [113.51]

82.* Smith C, Lowenthal LA: A study of elastic arteries in irradiated mice of different ages. Proc Soc Exp Biol Med 1950; 75: 859-61.

83. Zeitler E, Richter El, Roth FJ, Schoop W. Results of percutaneous angioplasty. Radiology 1983;146:57.

84. Wilson SE, Wolf GL, Cross AP. Percutaneous transluminal angioplasty versus operation for peripheral arteriosclerosis. J Vasc Surg 1989;9:1.

85. Krepel VM, vanAndel GJ, vanErp WF. Percutaneous transluminal angioplasty of the femoropopliteal artery: Initial and long-term results. Radiology 1985;156:325-8.

86. Gallino A, Mahler F, Probst P, Nachbur B. Percutaneous transluminal angioplasty of the arteries of the lower limbs: a 5-year follow-up. Circulation 1984;70:619-23.

87.* Hunink MGM, Donaldson MC, Meyerovitz MF, et al. Risks and benefits of fermoropopliteal percutaneous balloon angioplasty. J Vasc Surg 1993;17:183-94. [113.141]

88.* Rosen E, Goldberg K, Myrick K Levenson SE: Radiation survival of vascular smooth muscle cells as a function of age. Int J Radiat Biol 1985; 48: 71-9.

89.* Hopewell JW, Calvo W, Jeneke R, Reinhold HS, Robbins MEC, Whitehouse: I. Basic principles -- microvasculature and radiation damage. Recent Result Cancer Res 1993; 130: 1-16.

90.* Fajardo LF: The unique physiology of endothelial cells and its implication in radiobiology. Front Radiat Ther Oncol 1989; 23: 96-112.

91.* Hopewell JW, Calvo W, Campling D, Reinhold HS, Rezvani M, Yeung TK: Effects of radiation on the microvasculature -- implications for normal-tissue damage. Front Radiat Ther Oncol 1989; 23: 85-95.

92. * Johnstone PAS, Sprague M, DeLuca AM, Bacher JD, Hampshire VA, Terrill RE, Kinsella TJ, Sindelar WF: Effects of intraoperative radiotherapy on vascular grafts in a canine model. Int J Radiation Oncology Biol Phys 1994; 29: 1015-25.

93.* Tochner ZA, Pass HI, Sindelar WF, DeLuca AM, Grisell DL, Bacher JD, Kinsella: Long term tolerance of thoracic organs to intraoperative radiotherapy. Int J Radiation Oncology Biol Phys 1992; 22: 65-9.

94.* Stewart JR, Fajardo LF: Radiation-induced heart disease: an update. Prog Cardiovas Dis 1984; 27(3): 173-94.

95.* Mittal B, Deutsch M, Thompson M, Dameshek HL: Radiation-induced accelerated coronary arteriosclerosis. Am J Med 1986; 81: 183-4.

96.* Cross WG, Ing H, Freedman N: A short atlas of bets-ray spectra. Phys Med Biol 1983; 28(11): 151-60.

97.* Pattee PL, Johns PC, Chambers RJ: Radiation risk to patients from percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1993; 22: 1044-51.

98.* Jeans SP, Faulkner K, Love HG, Bardsley RA: An investigation of the radiation dose to staff during cardiac radiological studies. Brit J Radiol 1985; 58: 419-28.

99.* Cascade PN, Peterson LE, Wajszczuk WJ, Mantel J: Radiation exposure to patients undergoing percutaneous transluminal coronary angioplasty. Am J Cardiol 1987; 59: 996-7.

100.[a] Dimitrievich GS, Fischer-Dzoga K, Griem ML: Radiosensitivity of vascular tissue -- I. differential radioselectivity of capillaries: a quantitative *in vivo* study. Radiat Res 1984; 99: 511-35.

101.* Fischer-Dzoga K, Dimitrievich GS, Griem ML: Radiosensitivity of vascular tissue -- II. differential radioselectivity of aortic cells *in vitro* . Radiat Res 1984; 99: 536-46

102.* Sinclair WK: Cyclic x-ray responses in mammalian cells *in vitro* . Radiat Res 1968; 33: 620-43.

103.* Laird JR; Carter AJ; Kufs WM; Hoopes TG; Farb A; Nott SH; Fischell RE; Fischell DR; Virmani R; Fischell TA: Inhibition of neointimal proliferation with low-dose irradiation from a beta-particle-emitting stent. Circulation 1996 Feb 1;93(3):529-36

Abs: Fourteen titanium-mesh stents were implanted in the iliac arteries of nine NIH miniature swine. There were seven beta-particle-emitting radioisotope stents (32P, activity level 0.14 microCi) and seven control stents (31P, nonradioactive). There was a significant reduction in neointimal area (1.76 +/- 0.37 mm2 versus 2.81 +/- 1.22 mm2, P = .05) and percent area stenosis (24.6 +/- 2.9% versus 36.0 +/- 10.7%, P = .02) within the beta-particle-emitting stents compared with the control stents. Neointimal thickness, which was assessed at each wire site, was also significantly less within the treatment stents (0.26 +/- 0.04 mm versus 0.38 +/- 0.10 mm, P = .012). Scanning electron microscopy showed no excess inflammatory reaction or fibrosis in the media, adventitia, or perivascular space of vessels treated with the beta-particle-emitting stent compared with control vessels. At 28 days, there was no difference in smooth muscle cell proliferation as measured by the proliferating cell nuclear antigen index. Cardiology Service, Walter Reed Army Medical Center, Washington, DC

104.* Friedman M, Felton L, Byers S: The antiatherogenic effect of iridium192 upon the cholesterol-fed rabbit. J Clin Invest 1964; 43(2): 185-92.

105.* Hehrlein C, Stintz M, Kinscherf R, Schlosser K, Huttel E, Friedrich L, Fehsenfeld P, Kubler W: Pure β-particle-emitting stents inhibit neointima formation in rabbits. Circulation 1996; 93: 641-5.

106.* Stewart JR, Fajardo LF, Gillette SM, Constine LS:: Radiation injury to the heart. Int J Radiation Oncology Biol Phys 1995; 31(5): 1205-11.

107. * Hehrlein C, Gollan C, Donges K, Metz J, Reissen R, Fehsenfeld P, von Hodenberg E: Low-dose radioactive endovascular stents prevent smooth muscle proliferation and neointimal hyperplasia in rabbits. Circulation 1995; 92: 1570-5. d [113.107]

108.* Khan FM: Brachytherapy. chapter 15 in The Physics of Radiation Therapy -- Second Edition. Williams & Wilkins, Baltimore, MD, pgs 418-73.

109.* Waksman R; Robinson KA; Crocker IR; Gravanis MB; Palmer SJ, Wang C; Cipolla GD; Hillstead RA; King SB 3rd: Intracoronary radiation before stent implantation inhibits neointima formation in the stented porcine coronary arteries.Circulation 1995; 92: 1383-6. d [113.125]

110.* Liermann D, Schopohd B, Strassman G: Myointimal hyperplasia: long-term results of a pilot study of prophylactic endovascular radiation therapy in peripheral vessels. J Vasc Intervent Radiol 1995; Jan: 22.

111.* Liermann D, Bottcher HD, Goethe JW: Use of low dose local radiation for treatment of restenosis. Sixth Annual International Symposium Vascular Diagnosis Intervention 1994; Jan: 69-74.

112.* King SB, Waksmann R, Crocker I: Discoveries in Radiation for Restenosis. Emory University School of Medicine, Atlanta, GA, 1996, 142 pages.

Abs: Collects the 44 abstracts from the "first international workshop devoted to this exciting new field" presented by the Andreas Gruentzig and Cardiovascular Center and the Department of Radiation Oncology of the Emory University School of Medicine held at the JW Marriott Hotel. Atlanta, GA, January 11-12, 1996. There were 12 corporate sponsors and 35 faculty including Ralph Shuping and Bram Zuckerman. Topics included Incidence and mechanisms of restenosis; Radiobiology, pathology and Physics; Radiation for restenosis in animal models; Stents and radiation; Peripheral vascular disease; Clinical trials with endovascular radiation in coronary arteries; Industry approach; Economic and regulatory issues.

113.* King SB, Waksmann R, Crocker I: Discoveries in Radiation for Restenosis -- Selected Literature. Emory University School of Medicine, Atlanta, GA, 1996, 209 pages.

Abs: Collects 23 articles from the "first international workshop devoted to this exciting new field".

114.* Kuntz RE, Gigson CM, Nobuyoshi M, Baim DS: Generalized model of restenosis after conventional balloon angioplasty, stenting and directional atherectomy. J Am Coll Cardiol 1993; 21: 15-25. [113.2]

Abs: The restatement of the mathematical "bigger is better" hypotheses. "It is thus the immediate result (and not the procedure used to obtain that result) that determines late outcome after coronary intervention."

115.* Schwartz RS, Edwards WD, Bailey KR, Camrud AR, Jorgenson MA, Holmes DR: Differential neointimal response to coronary artery injury in pigs and dogs -- implications for restenosis models. Arterioscler Thromb 1994; 14: 395-400. [113.14]

116. * Wiedermann JG, Marboe C, Amols H, Schwartz A, 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; 25:1451-6. [113.80]

117.* Condado JA, Gurdiel O, Espinosa R, Brito JG, Burger B, Villoria G, Acquatella H, Liprie SF: Late follow-up after percutaneous transluminal coronary angioplasty (PTCA) and intracoronary radiation therapy (ICRT). ?J Am Coll Cardiol 1995 (abstract) [113.158]

Abs: Folks from Hospital Miguel Perez-Carreno, Venezuela report 6 mo f/u on 21 patients. Among 10 arteries receiving 2,500 cGy "tiny aneurysms" developed in 7, 1 anterioseptal MI, 1 aneurysm of the LAD. None of these problems among 12 arteries receiving 2,000 cGy.

Alphabetical by first author

58. Abbas MA, Benitz.. Comparative effects of single and fractionated doses of .. Clinical Research 1992
23. Abbas NA, Afshari NA.. Effect of x-ray irradiation on neointimal proliferation ..Clinical Research 1993
79. Annest LS, Anderson RP.. Coronary artery disease .. mediasteinal radiation . J Thorac Cardiovasc Surg 1983
72. Applefield MW, . Long term cardiovascular evaluation of patients with Hodgkin's .. Cancer Treat Rep 1982
4. Austin GE, Ratliff NB.. Intimal proliferation of smooth muscle cells as an explanation .. JACC 1985
6. Ayers DC, Evarts CM..The prevention of heterotopic ossification in .. J Bone Joint Surgery 1986
68. Bandyk DF. Postoperative surveillance of infrainguinal bypass. Surg Clin North Am 1990;70:71-85.
32. Berner BM, Wright AE, Gram W, Butler B: Arterial brachytherapy. Medical Physics 21: 96 (abstract) (1994
69. Blair JF, Bandyk DF. Real-time color Doppler in arterial imaging. ..Vascular Surgery. ..Saunders, 1991
29. Bottcher HD.. Endovascular irradiation.. stenosis Int J of Radiation Oncology, Biology and Physics 1994
75. Brosius FC.. Radiation heart disease -- analysis of 16 young necrops 3,500 rads to the heart. Am J Med 1981
50. Capek P, McLean GK.. Femoropopliteal angioplasty. Factors influencing long-term . Circulation 1991
99. Cascade PN, Peterson LE.. Radiation exposure to patients undergoing PTCA. Am J Cardiol 1987
2. Clowes AW, Reidy MA..: Mechanisms of stenosis after arterial injury. Laboratory Investigation 1983
117. Condado JA, Gurdiel O. Late follow-up after PTCA and ICRT. ?JJACC1995
66. Coran AG, Warren. Arteriographic changes in. femoropopliteal arteriosclerosis obliterans. N Eng J Med 1966
96. Cross WG, Ing H, Freedman N: A short atlas of bets-ray spectra. Phys Med Biol 1983; 28(11): 151-60.
12. Dawson JT. Theoretic considerations regarding low-dose radiation therapy..Texas Heart Institute Journal 1991
100. Dimitrievich GS.. Radiosensitivity of vascular tissue -- I. radioselectivity of capillaries.. Radiat Res 1984
5. Dunsmore LD, LoPonte MA, Dunsmore RA: Radiation-induced coronary artery disease. JACC 1986
26. Escarmont A..The treatment of 787 keloid scars by iridium 192 .. Int J Radiation Oncology Biol Phys 1993
90. Fajardo LF: The unique physiology of endothelial cells and its implication in . Front Radiat Ther Oncol 1989
55. Ferns GAA,.. Inhibition of neointimal smooth muscle accumulation after angioplasty .. Science 1991
30. Fischell TA, Bassam KK.. Low-dose beta particle emission from stent wire results Circulation 1994
56. Fischell TA, Kharma.. Low-dose, β-particle emission from "stent" wire results in .. Circulation 1994
16. Fischell TA..Low-dose irradiation inhibits clonal proliferation of smooth muscles.. Arterioscler Thromb 1991
101. Fischer-Dzoga K. Radiosensitivity of vascular tissue -- II. radioselectivity of aortic *in vitro* . Radiat Res 1984
1. Fonkalsrud EW.: Serial changes in .arterial radiation therapy. Surgery Gynecology and Obstetrics1977
62. Fontenla DP, Deor High dose rate intravascular brachytherapy for coronary artery restenosis.to AAPM 1996;.
53. Forrester A Fishbein M.. A paradigm for restenosis based on cell biology; clues for.. JACC 1991
104. Friedman M, Felt.. The antiatherogenic effect of iridium192 on the cholesterol-fed rabbit. J Clin Invest 1964
86. Gallino A.. Percutaneous transluminal angioplasty of the arteries of the lower limbs: a 5-y.. Circulation 1984
39. Gehman KE, .High dose rate endovascular irradiation Endocuritherapy/Hyperthermia Oncology 1994
14. Gellman J, Healey G..The effect of very low dose irradiation on restenosis following.. Circulation 1991
10. Gillette EL, Powers BE.. Response of aorta and branch arteries .. Int J Radiation Oncology Biol Phys 1989
74. Gold H: Production of arteriosclerosis in the rat -- effect of x-ray and a high fat diet. Arch Pathol 1961
67. Green RM. Annual Incidence of Infrainguinal Angioplasty at the U Rochester .. : 1995:
25. Hehrlein C, Zimmerman M.. Radioactive coronary stent implantation inhibits neointimal Circulation 1993
107. Hehrlein C, Gollan C.. Low-dose radioactive ..stents prevent..hyperplasia in rabbits. Circulation 1995
46. Hehrlein C, Kaiser S,..Effects of very low dose endovascular irradiation via an activated.. Circulation 1995
105. Hehrlein C, Stintz M.. Pure β-particle-emitting stents inhibit neointima in rabbits. Circulation 1996
15. Hermans WRM.. Prevention of restenosis after PTCA American Heart Journal 1991
91. Hopewell JW. Effects of radiation on the microvasculatnormal-tissue damage. Front Radiat Ther Oncol 1989
89. Hopewell JW..I. Basic principles -- microvasculature and radiation damage. Recent Result Cancer Res 1993

87. Hunink MGM,.Risks and benefits of fermoropopliteal percutaneous balloon . J Vascular Surgery 1993
65. Imparato AM, Kim GE, Davidson T, Crowley JG: Intermittent claudication: Its natural course. Surgery-1975
98. Jeans SP. An investigation of the radiation dose to staff during cardiac radiological studies. Brit J Radiol 1985
51. Jeans WD, Armstrong S.. Fate of patients undergoing transluminal angioplasty for.. Radiology 1990
52. Johnston KW. Femoral and popliteal arteries: reanalysis of results of balloon angioplasty. Radiology 1992
92. Johnstone PAS,.. Effects of intraoperative radiotherapy. in canine. Int J Radiation Oncology Biol Phys 1994
108. Khan FM: Brachytherapy. chap 15 in The Physics of Radiation Therapy .. Williams & Wilkins
112. King SB, Waksmann R, Crocker I: Discoveries in Radiation for Restenosis.. Atlanta, GA, 1996
113. King SB, Waksmann R, Crocker I: Discoveries.. Selected Literature. Atlanta, GA, 1996.
71. Kopelson G, Herwig KJ: The etiologies of coronary artery disease. Int J Radiation Oncology Biol Phys 1978
19. Koras SP, Gravanis .. Coronary intimal proliferation after balloon injury and stenting in swine. JACC 1992
9. Kovalic JJ, Perez CA: Radiation therapy following keloidectomy.. Int J Radiation Oncology Biol Phys 1989
85. Krepel VM, vanAnde.. Percutaneous transluminal angioplasty of the femoropopliteal artery:. Radiology 1985
114. Kuntz RE, Gigson..Generalized model of restenosis after.. angioplasty,.. J Am Coll Cardiol 1993
103. Laird JR; .: Inhibition of neointimal proliferation with low-dose irradiation a beta-.. stent. Circulation 1996
76. Lamberts HB, d: Contributions to ..VII. X-ray-induced atheromatous lesions .. rabbits. Int J Rad Biol ?1963
111. Liermann D, Bottcher . Use of low dose local radiation for.. of restenosis.Int Symp Vasc Dx Interven 1994
110. Liermann D, Schopohd. Myointimal hyperplasia: long-term results.. J Vasc Intervent Radiol 1995
36. Liermann D..Prophylactic endovascular radiotherapy to prevent intimal .Cardiovasc Intervent Radiol 1994
80. Lindsay S, Kohn HI.. Aortic arteriosclerosis in the dog after .. aortic x-irradiation. Circulation Research 1962
43. Ly NC, Whitincy JS.. A novel brachytherapy source for treatment of coronary Medical Physics 1995
35. Mazur W, Ali NM.. High dose rate intracoronary radiation suppresses neointimal Circulation 1994
7. McPherson DD, Armstrong M..High frequency epicardial echocardiography for coronary artery JACC1986
95. Mittal B, Deutsch M, Thompson M, Radiation-induced accelerated coronary arteriosclerosis. Am J Med 1986
27. Parvani SB, Scott WP..Management of pterygium with surgery .. Int J Radiation Oncology Biol Phys 1994
97. Pattee PL: Radiation risk to patients from percutaneous transluminal coronary . J Am Coll Cardiol 1993
20. Pellegrini VD..Prevention of heterotopic ossification with irradiation total hip.. J Bone Joint Surgery 1992
41. Popowski Y, Verin V.. High dose rate brachytherapy for Int J Radiation Oncology Biol Phys 1995
49. Popowski Y, Verin V..Intra-arterial Y90 brachytherapy: .. Int J Radiation Oncology Biol Phys 1995
73. Prentice RTW: Myocardial infarction following radiation, Lancet 1965; August 21: 388. (letter)
40. Prestwich WV, Kennett TJ, .. The dose distribution produced by a P32-coated stent. Medical Physics 1995
88. Rosen E, G. Radiation survival of vascular smooth muscle cells as a function of age. Int J Radiat Biol 1985
3. Rosen E,..Radiation survival properties of cultured vascular smooth muscle cells. Radiation Research 1984
54. Ross R. Pathophysiology of atherosclerosis. In: Vascular Surgery McGraw Hill, 1994
42. Sarac TP, Riggs PN,.. The effects of low dose radiation on neointimal hyperplasia. J Vas Surg 1995
57. Schopohl B. Endovascular Radiation in peripheral vascular ... In: Discoveries in radiation for restenosis 1996
115. Schwartz RS, Edwards .. Differential neointimal response to coronary injury .. Arterioscler Thromb 1994
17. Schwartz RS, Koval TM.. Effect of external beam irradiation on neointimal .. JACC 1992
11. Schwartz RS, Murphy JG..Restenosis after balloon angioplasty: Circulation 1990
24. Shefer A, .. Suppression of intimal proliferation after balloon angioplasty with local beta.. JACC 1993
28. Shimotakahara S; Mayberg MR Gamma irradiation inhibits neointimal hyperplasia in rats .. Stroke 1994
102. Sinclair WK: Cyclic x-ray responses in mammalian cells *in vitro* . Radiat Res 1968; 33: 620-43.
82. Smith C, LowentA study of elastic arteries in irradiated mice of different ages. Proc Soc Exp Biol Med 1950
81. Soares CG Measurement of radial dose.. small beta emitters.. radiochromic foil.. Radiat Prot Dosim 1993
18. St Goar FG, Pinto FJ.. Detection of coronary atherosclerosis in young adult .. Circulation 1992
13. St Goar FG, Pinto FJ.. Intravascular ultrasound imaging of angiographically normal ..JACC 1991
77. Stewart JR, Cohn KE, Fajardo LF, Hancock EW, : Radiation-induced heart disease. Radiology 1967
106. Stewart JR, Fajardo LF, Radiation injury to the heart. Int J Radiation Oncology Biol Phys 1995
94. Stewart JR, Fajardo LF: Radiation-induced heart disease: an update. Prog Cardiovas Dis 1984; 27(3): 173-94.
8. Sylvester JE, ..The use of postoperative irradiation for the preventio Int J Radiation Oncology Biol Phys1988
48. Teirstein PS, Massullo V.. Catheter-based radiation therapy to inhibit restenosis following ..Circulation 1995
60. Teirstein PS. Endovascular radiation in human coronary arteri. In: Discoveries in radiation for restenosis 1996
93. Tochner ZA.Long term tolerance of thoracic organs to .. Int J Radiation Oncology Biol Phys 1992
63. Veith FJ, Panetta TF.. Femoralpopliteal-tibial occlusive disease. In: Vascular Surgery: McGraw-Hill 1994

78. Voivin JF, Hutchinson Coronary heart disease mortality after irradiation for Hodgkin's Disease. Cancer 1982
59. Waksman R.. Endovascular low-dose irradiation inhibits neointimal formation.. Circulation 1995
47. Waksman R.. Intracoronary low dose beta .. irradiation inhibits neoint.. Circulation 1995
45. Waksman R.. Efficacy and safety of beta versus gamma radioisotopes for .. Circulation 1995
34. Waksman R.. Endovascular irradiation inhibits a restenosis-like response.. Circulation 1994
61. Waksman R.. Endovascular radiation therapy for restenosis. 8th Internat Brachytherapy Conference.: 1995
109. Waksman R.. Intracoronary radiation before stent implantation inhibits..Circulation 1995
64. Werber J, Sood BM.. Tolerance of the Carotid Sheath Contents to Brachytherapy. Laryngoscope 1991
38. Wiedermann JG, Leavy .. Effects of high-dose intracoronary Am J Physiology Heart Circ. Physiology 1994
21. Wiedermann JG, Leavy J, Amols H, Homma S, DiTullio K, Sherman D, Apfelbaum K, ..Circulation 1992
37. Wiedermann JG, Marboe C.. Intracoronary irradiation markedly reduces restenosis after Circulation 1994
31. Wiedermann JG, Marboe C.. Intracoronary irradiation markedly reduces restenosis.. JACC 1994
116. Wiedermann JG, Marboe.. Intracoronary irradiation markedly reduces neointimal J Am Coll Cardiol 1995
33. Wiedermann JG, Marboe.. Intracoronary irradiation.- minimal effective dose for prevention Circulation 1994
44. Wiedermann JG.. Intracoronary irradiation fails to reduce neointimal proliferation after.. Circulation 1995
22. Wilder RB, Buatt JK..Pterygium treated with excision Int J Radiation Oncology Biol Phys 1992
84. Wilson SE.. Percutaneous transluminal angioplasty versus operation for peripheral . J Vasc Surg 1989
83. Zeitler E, Richter El, Roth FJ, Schoop W. Results of percutaneous angioplasty. Radiology 1983;146:57.

Attachment C. NRC Regulations and Requirements Relating to Brachytherapy Treatment of Restenosis

Currently, 10 CFR Part 35, *Medical Use of Byproduct Material* does not permit the use of brachytherapy sources for intravascular uses. Therefore, these treatments currently could only be performed under a broad scope license or at a facility with a limited specific license which has received an exemption from the requirements of 10 CFR 35.400, *Use of Sources for Brachytherapy.*

Broad Scope License

Many broad scope licensees are authorized to use isotopes with atomic numbers 3-83 for medical research, diagnosis and therapeutic uses in individual quantities not to exceed 1 curie. These licensees would be authorized to perform medical research into brachytherapy treatment of restenosis, provided that the licensee complies with the requirements of 10 CFR 35.6, Provisions for Research Involving Human Subjects. These licensees should be reminded that, for any research not conducted, funded, supported, or regulated by a Federal Agency that has adopted the Federal Policy, the licensee must apply, in accordance with 10 CFR 35.6, for a specific amendment before conducting research involving human subjects. Additionally, some broad scope licenses are written to restrict the use of brachytherapy sources to the treatment of cancer; therefore, use of the sources for treatment of restenosis would require an amendment to the license. Broad scope licensees should review the authorizations for the use of brachytherapy sources on their licenses.

Limited Specific License

Limited specific licensees seeking authorization to perform these procedures must apply for an exemption from the requirements of 10 CFR 35.400, *Use of Sources for Brachytherapy.* This application must address the training and experience of the individuals involved in treatment delivery. Individuals performing these treatments must either meet the training and experience requirements of 10 CFR 35.940, *Training for Use of Brachytherapy Sources*, or be supervised by such an individual. It is anticipated that due to the complexity of these procedures, a team approach will be used, which would include a radiation oncologist, a cardiologist, an interventional radiologist, a medical physicist, etc.

Licensing Remote Afterloading Devices

In addition to the requirements regarding brachytherapy found in 10 CFR Part 35, licensees wishing to use remote afterloading brachytherapy units may need to address additional requirements found in *Policy and Guidance Directive FC 86-4., Information for Licensing Remote Afterloading Devices.* These requirements include establishing provisions to perform emergency surgical procedures for the removal of dislodged sources within the patient and the presence of an authorized user physician, radiation safety officer, or medical physicist during the treatment of the patient.

Specific questions relating to NRC regulations and requirements may be referred to James Smith, 301-415-7904

Attachment D. Informed Consent -- Required Elements

Elements expected in the informed consent include:

1.__ a statement that the study involves research

2.__ an explanation of the purposes of the research

3.__ the expected duration of the subject's participation

4.__ a description of the procedures to be followed

5.__ identification of any procedures which are experimental

6.__ a description of any reasonably foreseeable risks or discomforts to the subject

7.__ a description of any benefits to the subject or others

8.__ a disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the subject

9.__ a statement describing the extent to which confidentiality of the subject's records will be maintained and that notes that FDA may inspect the records

10.__ an explanation as to whether any compensation and/or medical treatments are available if injury occurs and, if so, what they consist of or sources of further information

11.__an explanation of whom to contact for answers to questions about the study and the subject's rights and whom to contact in the event of a research-related injury

12.__ a statement that participation is voluntary and that subjects may refuse to participate or discontinue participation at any time without penalty or loss of benefits

When appropriate:

13.__ a statement that the procedure or treatment may involve unforeseeable risks to subject, or to the embryo or fetus should the subject become pregnant

14.__ anticipated circumstances under which the investigator may terminate the subject's participation without regard to the subject's consent

15.__ any additional costs to subject as a result of participation

16.__ consequences of a subject's decision to withdraw and procedures for withdrawal

17.__ a statement that significant new findings which may relate to the subject's willingness to participate will be provided to the subjects

18.__ the approximate number of subjects involved in the study

Revision history -- Brachytherapy Guidance

3/11/96 - bibliography development, John, Ralph, Dan

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