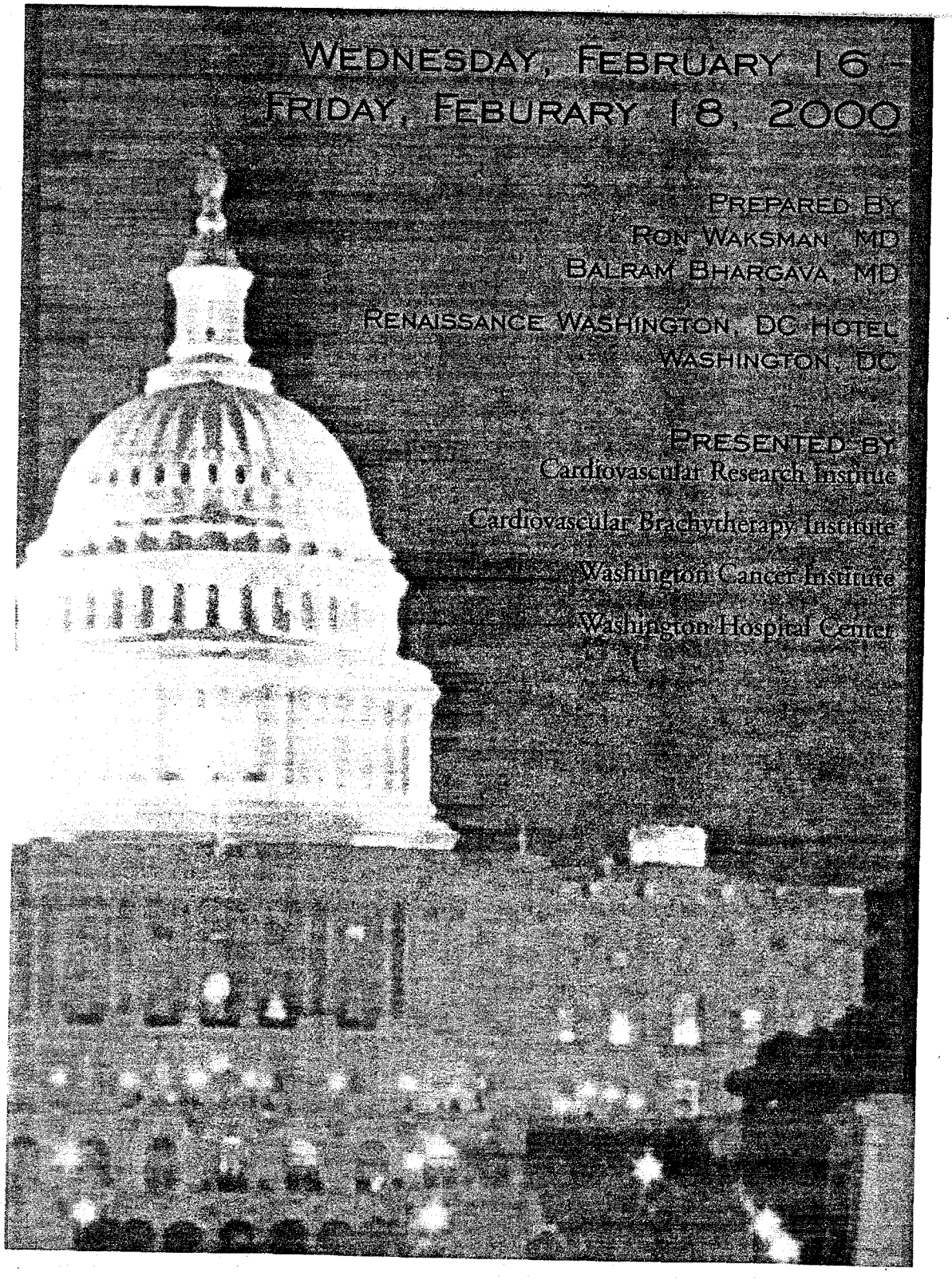
CARDIOVASCULAR RADIATION THERAPY IV

SYLLABUS



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PREPARED BY
RON WAKSMAN, MD
BALRAM BHARGAVA, MD

RENAISSANCE WASHINGTON, DC HOTEL
WASHINGTON, DC

PRESENTED BY
Cardiovascular Research Institute
Cardiovascular Brachytherapy Institute
Washington Cancer Institute
Washington Hospital Center

RADIANT™ Liquid Isotope Intravascular Radiation Therapy System

by Neal Eigler MD, James Whiting PhD, Raj Makkar MD, Hidehiko Honda MD, FF (Russ) Knapp PhD, Frank Litvack MD, Alex Li. MS

Device

RADIANT™ is manufactured by United States Surgical Corporation, Vascular Therapies Division, (formerly Progressive Angioplasty Systems). The system comprises a liquid β-radiation source, a shielded isolation/transfer device (ISAT), modified over-the-wire or rapid exchange delivery balloons, and accessory kits. The liquid β-source is Rhenium-188 in the form of sodium perrhenate (NaReO4). Re-188 is primarily a β-emitter with a physical half-life of 17.0 hours. The maximum energy of the β- particles is 2.1 MeV. The source is produced daily by the nuclear pharmacy "hot lab" by eluting a Tungsten-188/Rhenium-188 generator manufactured by Oak Ridge National Laboratories (ORNL). Using anion exchange columns and Millipore filters the effluent is concentrated to approximately 100 μCi/ml, calibrated, and loaded into the (ISAT) which is subsequently transported to the cardiac catheterization laboratory. The delivery catheters are modified over-the-wire, and rapid exchange stent delivery balloons. These balloons have thickened polyethylene walls to augment puncture resistance; additional shielding, dual radioopaque markers and specially configured self-sealing connectors.

Proposed Indications

The RADIANT system will be evaluated for efficacy to prevent restenosis following balloon angioplasty or stenting patients with de novo or restenotic lesions. The planned U.S. trial is called The Radiation Angioplasty Trial (RADIANT). The "RADIANT" Phase-I study is designed as a pilot study to preliminarily evaluate safety/efficacy of intravascular radiation delivery to prevent restenosis. The pivotal study to follow will be a multicenter randomized double blinded placebo controlled design.

Procedure

Radiation therapy is performed immediately after successful balloon angioplasty or stenting, with the guidewire left in position. A RADIANT™ catheter of the same diameter as the last PTCA balloon used is selected. Prior to insertion, the radiation delivery catheter is tested for integrity to hold air and maintain vacuum. The balloon is positioned in the coronary artery prior to charging it with isotope. Serial inflations at 3 ATM are performed until the prescribed dose has been given (ranging from 6 to 10 minutes total inflation time).

Limitations of Current Intravascular Radiation Delivery Methods

Current catheter-based radiation systems have limitations that the RADIANT™ system was designed to address. These limitations can be categorized into problems of dose delivery to the target tissue, patient safety, and personnel safety.

Distal and tortuous coronary segments may be untreatable if catheter diameter or stiffness preclude safe access to these locations. The RADIANT™ delivery catheter performs identically to its parent generation PTCA balloons and can reach any portion of the coronary anatomy treatable with balloon angioplasty. Thus vessel segments 20 to 40-mm in length, previously expanded with balloons ranging in diameter from 2 to 4 mm are potentially treatable. Moreover, the device is compatible with 0.064" lumen 6F guiding catheters.

Whether treated with sealed sources or an afterloaded wire, IVUS examination may be needed to specify dose. This approach is expensive and time-consuming. IVUS gives a rough estimate of how far off center the delivery catheter will be, and the distance from the source to the target(s). Dose calculation must also address the problem of cold spots between sources and hot spots due to even small degrees of off centering by as little as 0.5-mm. Even if centered to within 0.5 mm, doses at a prescribed depth will typically vary by a factor of 4. Such variations in dosimetry may limit the therapeutic range of dose specification for these systems.

Dose prescription with the RADIANT™ system is straightforward. The RADIANT™ balloon size is matched to the largest balloon size used for PTCA or stent delivery, guaranteeing that the delivery balloon make contact with the vessel wall or the stent when expanded with isotope. A dose at a prescribed radial distance from the expanded balloon is selected. The total duration of balloon inflation is determined by the activity concentration of the liquid source, the time elapsed after source calibration, and the diameter of the chosen delivery balloon. IVUS guided dosimetry is neither helpful nor necessary. The RADIANT™ balloon is by definition "centered" with respect to the lumen. There are no "hot spots." "Cold spots" due to bubbles or off centered guidewire lumen can cause at worst a 10% reduction in dose to a localized portion of the irradiated tissue. Finally, the dose distribution surrounding a liquid filled balloon is the most homogeneous of any of the currently devised seed or wire type systems.

With respect to patient safety issues there are several concerns: ischemic complications, long term effects at the treatment site, total patient exposure, and embolization of a radiation source. Ischemic complications may result from device trauma, device stimulation of thrombosis, the physical obstruction of flow by the system, the coronary artery dwell time, and the quality of patient monitoring available. The RADIANT™ method consisting of intermittent low-pressure balloon inflations from a low profile, small shaft diameter, PTCA catheter is frequently the standard operating procedure during routine balloon angioplasty.

The incidence and time course of long-term effects at the treatment site, including aneurysm formation or enhanced atherogenesis are not fully known with any intravascular radiation device. To the extent that these sequelae are dose-dependent, the RADIANT™ method offers a potential advantage in eliminating dose "hot spots" and minimizing "cold spots". This has the advantage of extending the therapeutic range for dosing to achieve the desired effect without sequelae due to overdosage.

Source embolization is the most dreaded complication. Although loss of an afterloaded Ir-192 source should be extremely rare, breakage of a wire or a catheter is a known complication of angioplasty. Such a loss would likely be catastrophic and/or represent a considerable exposure risk to personnel attempting to retrieve it. Loss of the RADIANT™ balloon Re-188 liquid source in a coronary artery should also be a rare event for several reasons. Inflation pressures are kept at least four standard deviations below the mean burst pressure, thus the expected frequency of balloon rupture is less than 1 in 30,000 catheters. The chances of balloon rupture are further minimized by the protocol which calls for successful prior full expansion of a PTCA balloon of the same diameter in the same lesion to at least 6 ATM (12 ATM if a stent has been placed). Moreover, every RADIANT™ catheter is pressure tested with air to rated burst pressure immediately prior to insertion and before charging with radioisotope. The worst case scenario is defined as rupture of a 4.0 mm diameter by 40 mm long balloon, discharging its entire isotope contents into the coronary artery. Dilution of the isotope in blood is nearly instantaneous resulting in an organ distribution pattern similar to intravenous injection. Organs with the highest exposure are the stomach, large and small bowel, and the thyroid. These exposures are similar to a single fractionated radiation therapy treatment and no short term and only rare long-term stochastic sequelae are expected.

Personnel safety is the final limitation of intravascular radiation therapy. γ-Systems such as the Ir-192 exposes the radiation oncologist to approximately 10 to 20 μRem per hour. Although these exposure rates have been compared to fluoroscopy during interventional procedures, it should be remembered that standard 0.5 mm-lead equivalent radiation protective devices are virtually worthless in absorbing the high-energy gamma's of Ir-192. Direct handling of an Ir-192 source is exceedingly dangerous.

IVUS: IVUS was performed in 31/32 vessels excluding only the totally occluded RCA described above. Table 2 summarizes the IVUS results. Stent area was not significantly different between groups. Lumen area, intimal area and percent area stenosis all improved in a dose-related fashion.

Table 1 QCA parameters at 4 weeks after treatment

Dose (Gy)	0	16	22	29
n	8	8	8	8
Reference diameter (mm)	2.4±0.3	2.3±0.2	2.2±0.3	2.5±0.2
MLD (mm)	1.0±0.7	1.3±0.7	1.2±0.7	1.9±0.8*
Mean instent diameter (mm)	1.7±0.6	2.3±0.4	2.6±0.4*	2.8±0.3‡
% diameter stenosis	61±26	45±31	46±34	23±31*
Mean % diameter stenosis	30±20	4±18†	-12±19‡	-13±12‡

*p<.02, †p<.01, ‡p<.001 vs. control

Table 2. IVUS parameters at 4 weeks after treatment

Dose (Gy)	0	14	18	22
n	8	8	7	8
Stent area (mm2)	8.3±1.2	9.0±1.5	8.9±0.5	9.3±1.4
Lumen area (mm2)	4.4±1.2	7.0±1.8†	7.1±1.8†	7.6±1.6‡
Intimal area (mm2)	3.9±1.9	2.1±1.4*	1.8±1.4*	1.7±0.9†
Percent area stenosis	45±19	23±15*	21±18*	18±10†

*p<.05, †p<.01, ‡p<.001 vs. control

Histology

Figure 1 shows a graph of visually estimated percent area stenosis vs. dose. Area stenosis declined monotonically with increasing dose. All three radiation treated groups differed significantly from controls ($p<.027$). At the maximum dose percent stenosis was reduced by 64% compared to controls. There were no thrombosed vessels or organizing mural thrombi seen in any of the sections.

Radiation affected several features of neointimal histology. Control vessel neointima was highly cellular composed of predominantly smooth muscle cells. Radiation appeared to have a dose-dependent affect on cellularity ($p=.015$). At the maximum radiation dose, the neointima was judged to be acellular in 50% of the sections, although when cellular, the predominant cell type resembled control vessel type smooth muscle cells. Extracellular matrix (pink staining material) was reduced by radiation ($p=.015$). The most striking effect of radiation was an increase in the extent of fibrinoid (blue staining) material surrounding the lumenal sides of the struts ($p<.0001$). Minimal focal peri-strut foreign body giant cell and rare mononuclear inflammatory cells were present in the majority of control and irradiated sections.

There was no medial fibrosis or inflammation in any of the sections. There was occasional focal medial necrosis, which was slightly more common in the irradiated vessels but in no circumstances was there diffuse necrosis. Fibrosis in the form of adventitial thickening was seen more frequently in the irradiated segments ($p=.05$). In all sections the vasovasorum appeared normal.

In summary, radiation prior to stenting appears to have dose-dependent effects to limit neointimal formation by inhibition of smooth muscle cell proliferation resulting in less matrix deposition and a larger lumen. Marked increases in fibrinoid material are reminiscent of earlier stages of vascular healing and suggest that the proliferative phase of vascular healing may be attenuated or even arrested. The tunica media and adventitial vasovasorum are well preserved, suggesting that these doses may be well tolerated at least in the short term. The available data are consistent with the previously reported experience using Sr-90 seeds followed by stent injury in a pig coronary model. They show a substantial and significant dose-related improvement with concordant findings by QCA, IVUS, and histology. Experience using the Radiant™ in 32 coronary arteries revealed no unanticipated or adverse device handling or safety issues. Similar animal experiments evaluating the RADIANT™ system after balloon over-stretch injury, after stent placement, treatment of serial tandem radiated segments and bifurcation exposures are on going. First human clinical trials are slated for early 1998.