From the New England Society for Vascular Surgery

High dose-rate brachytherapy for the treatment of lower extremity in-stent restenosis

Karen J. Ho, MD,[a] Phillip M. Devlin, MD,[b] Arin L. Madenci, MD, MPH,[c] Marcus E. Semel, MD, MPH,[c] Edwin C. Gravereaux, MD,[c] Louis L. Nguyen, MD, MPH, MBA,[c] Michael Belkin, MD,[c] *and* Matthew T. Menard, MD,[c]
Chicago, Ill; and Boston, Mass

ABSTRACT

Objective: Historically, edge stenosis and late thrombosis limited the effectiveness of adjunctive endovascular brachytherapy (EVBT) for in-stent restenosis (ISR) after percutaneous transluminal angioplasty (PTA) and stenting. We evaluated an updated protocol of PTA and EVBT for ISR among patients with lower extremity occlusive disease.

Methods: This is a retrospective, single-center review of patients treated with PTA and EVBT for ISR in the iliac and femoropopliteal segments between 2004 and 2012. A dose of 20 Gy was given at a depth of 0.5 mm beyond the radius of the largest PTA balloon using iridium 192, with at least 2-cm-long margins of radiation coverage proximal and distal to the injured area. Stents were assessed for patency by duplex ultrasound imaging at 1, 3, 6, 9, 12, and 18 months and then yearly. The primary end point was freedom from ≥50% restenosis in the treated segment at 6 months, 1 year, and 2 years. Patency data were estimated using the Kaplan-Meier method. Secondary end points were early and late thrombotic occlusion.

Results: Among 42 consecutive cases in 35 patients of EVBT for ISR in common or external iliac (9 [20.8%]) and superficial femoral or popliteal (33 [76.7%]) arteries, or both, 21 patients (50%) had claudication, asymptomatic hemodynamically significant stenoses were identified on duplex ultrasound imaging in 16 (38.1%), and 4 (9.8%) had critical limb ischemia. Mean treated length was 23.5 ± 12.3 cm over a mean duration of 16.1 ± 9.6 minutes. There was one technical failure (2.3%). Median post-EVBT follow-up time was 682 days (range, 1-2262 days). There were two (4.9%) and five (11.9%) cases of early and late thrombotic occlusions, respectively. There was one death, believed to be secondary to acute coronary syndrome. Primary, assisted primary, and secondary patency in the entire cohort was 75.2%, 89.1%, and 89.1%, respectively, at 1 year and 63.7%, 80.6%, and 85.6%, respectively, at 2 years.

Conclusions: This contemporary protocol of PTA and adjunctive EVBT for lower extremity ISR, which is updated from those used in prior trials and includes a surveillance strategy that identifies at-risk stents for reintervention before occlusion, may be a promising treatment for lower extremity ISR at institutions where a close collaboration between vascular surgeons and radiation oncologists is feasible. (J Vasc Surg 2016;■:1-10.)

Purported mechanisms of failure of percutaneous transluminal angioplasty (PTA) of lower extremity arterial occlusive disease include immediate elastic recoil, acute thrombosis, neointimal hyperplasia, and late vascular remodeling.[1,2] Although PTA with stenting prevents elastic recoil and constrictive remodeling, in-stent restenosis (ISR), a consequence of neointimal hyperplasia, is a pervasive problem.[3] A wide array of strategies are currently available to address ISR, including drug-coated balloons (DCB), drug-eluting stents (DES), cutting balloon angioplasty, stent grafts, atherectomy, and surgical bypass. No one of these strategies has yet been proven to be the definitive treatment for ISR.[4]

Endovascular brachytherapy (EVBT), or the local intraluminal application of radiation from beta or gamma sources to a target vessel, is another strategy that mitigates neointimal hyperplasia.[1,5,6] Numerous early efforts examining the effect of EVBT in the treatment of de novo lesions[7-9] and in the prevention of restenosis (prophylaxis) after PTA[10-13] and PTA with stenting[14-17] were limited by edge stenosis and late stent thrombosis. More recent reports have had more promising results.[18,19]

In this study, we retrospectively evaluate the effectiveness of adjunctive EVBT to sustain the patency of PTA treatment of ISR in the iliac, superficial femoral artery (SFA), and popliteal artery segments using an updated protocol for iridium 192 (^{192}Ir) gamma irradiation at a high dose rate. Key aspects of our revised protocol include a higher dose of radiation, an extension of the safety margin of radiation coverage proximal and distal to the injured area by at least 2 cm, and a customized

From the Division of Vascular Surgery, Northwestern University Feinberg School of Medicine, Chicago[a]; and the Department of Radiation Oncology,[b] and Division of Vascular and Endovascular Surgery,[c] Brigham and Women's Hospital, Boston.

Author conflict of interest: none.

Presented at the Fortieth Annual Meeting of the New England Society for Vascular Surgery Annual Meeting in Stowe, Vt, September 27-29, 2013.

Correspondence: Matthew T. Menard, MD, Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, 75 Francis St, Boston, MA 02115 (e-mail: mmenard@partners.org).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

http://dx.doi.org/10.1016/j.jvs.2016.10.002

depth calculated from the radius of the largest PTA balloon used.

METHODS

Study population. This is a retrospective cohort review of PTA and adjunctive EVBT for ISR in the iliac, SFA, and popliteal artery segments performed at Brigham and Women's Hospital (Boston, Mass) between November 2004 and November 2012. This study was approved by the Institutional Review Board. Need for informed consent was waived.

Periprocedural and procedural details. The study included all patients in the Division of Vascular and Endovascular Surgery who underwent PTA and adjunctive EVBT for ISR in the iliac, SFA, and popliteal artery segments during the study period. All patients were treated in the standard manner of the practice of their vascular surgeon (M.T.M., E.C.G., and L.L.N.). Patients with recurrent symptoms or hemodynamically significant lesions ascribed to ISR identified by duplex imaging and associated with an ankle-brachial index (ABI) decrease ≥0.15 were preferentially treated with repeat PTA and adjunctive EVBT. Long-segment (≥20 cm) stent occlusions were typically treated with surgical bypass.

If the combination of patient history, physical examination findings, and duplex ultrasound imaging was suggestive of ISR, the patient was referred to the radiation oncologist for evaluation, informed consent was obtained, and the brachytherapy suite was reserved in advance. The patient was made aware that the final decision to undertake brachytherapy would be contingent on the angiographic findings on the day of the planned treatment. An ISR lesion was distinguished from residual stenosis by comparing the confirmatory angiographic images to those from the original stenting procedure.

All procedures were undertaken in a collaborative fashion by a board-certified vascular surgeon and radiation oncologist. Procedures were performed under conscious sedation supplemented with local anesthesia to the arterial access site. Retrograde contralateral femoral access was used in most cases, although brachial access was used on several occasions involving ISR of the iliac arteries in patients with dense groin scarring.

After a diagnostic arteriogram was performed, a 6F guiding sheath was introduced, the patient was systemically anticoagulated with heparin, the ISR lesion was crossed with a wire, and PTA was performed within the area of ISR. Additional PTA was undertaken to treat edge stenosis or new lesions in adjacent arterial segments if deemed necessary by the treating vascular surgeon. Adjacent new lesions were occasionally stented, also at the discretion of the treating vascular surgeon.

Once an angiographically satisfactory result (residual stenosis ≤30% and no evidence of dissection) was obtained, the wire was removed and a blind-ended, 150-cm-long, 6F high-dose rate brachytherapy catheter was placed. All angioplasty images and anatomic landmarks were reviewed, followed by placement of a calibrated brachytherapy "dummy strand" within the brachytherapy catheter to assist in precise intravascular measurement. The catheter and dummy strand were advanced across the angioplastied segment until the tip was 2 to 3 cm distal to the distal margin of the angioplastied segment (Fig 1). These 2- to 3-cm-long margins were used to address potential uncertainty in the exact position of the balloon and to allow for slight "watermelon seeding" and the tapering off of the radiation dose at the ends of the treatment zones. The sheath tip was withdrawn to the arterial segment proximal to the angioplastied segment to minimize the risk of sheath-induced thrombosis during the EVBT portion of the procedure.

Fluoroscopic images of the final position of the catheter and dummy strand were taken, and the length of the treatment was determined by the length of all angioplastied segments and the margins. Careful note was made of the largest balloon diameter deployed. The distance from the catheter for the 100% isodose line was determined to be the radius of the largest balloon plus 0.5 mm. The treatment depth of 0.5 mm beyond the radius of the largest PTA balloon was chosen to avoid overdosing smaller-than-average vessels and underdosing larger-than-average vessels and was based on normal clinical physics recommendations to be as specific as possible to the clinical target of radiation. The sheath and brachytherapy catheter were secured with sutures, an activated clotting time level >250 seconds was confirmed, and a heparin infusion of 500 units/hour was started via a peripheral intravenous catheter. The patient was transported to the EVBT suite on a stretcher by a nurse, and one-on-one nursing care was continued through the duration of the EVBT procedure.

EVBT was planned with a dedicated computer-assisted treatment planning system and was performed with a remote afterloader with a high dose rate. In brief, the remote afterloader is a machine that houses a single high-activity ^{192}Ir isotope that is welded to a cable and driven by a computer to preset locations based on treatment planning for optimized amounts of time to deliver a safe and graphically optimized uniform radiation treatment to the clinical target of the vessel wall. A dose of 20 Gy was prescribed to give a treatment depth of 0.5 mm beyond the radius of the largest PTA balloon. The dose of 20 Gy was selected because of treatment failures in prior published trials using 14 Gy.[8,16,17,20] Furthermore, 20 Gy has previously been used with demonstrated safety and efficacy in intracoronary brachytherapy.[21] The ^{192}Ir source was delivered in a stepwise manner to cover the entire angioplastied segment and an additional safety margin