External Beam Radiation to Prevent Restenosis After Superficial Femoral Artery Balloon Angioplasty

Eric Therasse, MD; David Donath, MD; Jacques Lespérance, MD; Jean-Claude Tardif, MD; Marie-Claude Guertin, PhD; Vincent L. Oliva, MD; Gilles Soulez, MD

Background—Femoropopliteal percutaneous transluminal angioplasty (PTA) remains limited by restenosis. Although vascular brachytherapy may be effective in reducing restenosis, external beam radiation would be more practical to administer after PTA.

Methods and Results—After femoropopliteal PTA without stent placement, 99 patients were randomly assigned to 0 Gy (placebo; n=24), 7 Gy (n=24), 10.5 Gy (n=26), or 14 Gy (n=25) of external beam radiation of the PTA site (with a 3-cm margin at both extremities) in 1 session 24 hours after PTA. The primary end point was minimum lumen diameter on quantitative angiography 1 year after PTA. One year after PTA, the mean minimum lumen diameter was 1.92, 1.64, 1.92, and 2.91 mm, respectively, for the 0-, 7-, 10.5-, and 14-Gy groups (P=0.0072 for 0 versus 14 Gy). Mean luminal loss was 1.14, 1.27, 1.08, and 0.14 mm, respectively, for the 4 groups (P=0.0072 for 0 versus 14 Gy). Restenosis >50% was present in 50%, 65%, 48%, and 25% of patients, respectively, for the 0-, 7-, 10.5-, and 14-Gy groups (P=0.072). At 18 months, repeated revascularizations were required in 25% of patients in the 0-Gy group versus 12% of patients in the 14-Gy group (P=0.24).

Conclusions—A single session of external beam radiation of 14 Gy of the femoropopliteal angioplasty site significantly reduces restenosis at 1 year. (Circulation. 2005;111:3310-3315.)

Key Words: claudication ■ peripheral vascular disease ■ angioplasty ■ restenosis ■ prevention

Percutaneous transluminal angioplasty (PTA) has a high technical success rate for the treatment of coronary and peripheral arterial obstructive diseases, but the long-term results are poor, mainly because of restenosis. Although bare and drug-eluting stents have reduced the incidence of restenosis in coronary arteries, they have had a much more limited impact at the femoropopliteal level.1–6 This situation has created the impetus to evaluate other preventive approaches. Among those evaluated, radiation therapy has proven to be effective in the coronary and superficial femoral arteries.7–9 Until now, brachytherapy has been the sole method of administering radiation therapy that has demonstrated success in limiting restenosis after PTA in humans. However, vascular brachytherapy is cumbersome and not widely used.

External beam radiation (EBR), in comparison with brachytherapy, may present many advantages in the prevention of restenosis after PTA for peripheral arterial disease. EBR does not have to be delivered immediately after balloon angioplasty and, therefore, does not interfere with or prolong the procedure. It does not require larger introducer sheaths, occluding centering mechanisms, or additional medical devices that are used with brachytherapy. In addition, EBR dosimetry is more precise and is not affected by lesion eccentricity or calcification. However, the effectiveness and optimal dose of EBR to prevent restenosis after PTA are unknown and are difficult to extrapolate from the experience with brachytherapy.

The primary objective of this study was to evaluate whether EBR can prevent restenosis after femoropopliteal PTA in comparison with a control group treated only with PTA. The secondary objectives were to assess the safety and dose-effect relation of EBR on restenosis.

Methods

Study Design and Study Population
The study was designed as a prospective, randomized, dose-finding trial, and its primary end point was minimum lumen diameter within the dilated arterial segment at 12 months, as measured by quantitative angiography.

Between July 1998 and March 2002, 122 patients were considered for inclusion in this study. Among these, 23 patients were excluded for various reasons: The referring physicians did not want the patient to participate in the study (3 patients), the patients did not meet the inclusion criteria (14 patients), the patients refused to participate in the study (5 patients), and the PTA had to be done on an emergency basis before the scheduled protocol procedure (1 patient). Ninety-nine patients were thus enrolled in the trial. These patients were
referred for PTA by their physicians (internists and vascular surgeons) because they had symptomatic, lifestyle-limiting vascular insufficiency, either claudication or critical ischemia (rest pain, ischemic ulcer, or gangrene) secondary to a de novo atherosclerotic obstructive lesion of the femoropopliteal artery. Patients were eligible to enter the trial if they had a stenosis or occlusion of the femoropopliteal artery with a diameter reduction of 50% or more and an ankle-brachial index ≤0.9. There were no limits on lesion length for entrance into the trial, so long as patients were considered eligible for PTA, after consideration of other clinical and angiographic data. Patients were deemed ineligible if they were <45 years of age, were women of child-bearing age, or had received a radiosensitizing agent or radiation therapy to the lower limb in the past. Patients were also not eligible if a stent had been previously implanted or needed to be implanted or if they had residual stenosis >50% after PTA. Approval of this study was obtained from the Scientific Review and Ethics Committees of our institutions with acknowledgement from the Health Protection Branch of the Health and Welfare Department of the Government of Canada. All eligible patients who accepted participation gave their written, informed consent after the goals and steps of the study had been explained to them.

**Angioplasty Procedure and Irradiation Methods**

All femoropopliteal PTA were performed under local anesthesia. Dilation diameter was chosen on the basis of the diameter of normal arterial segments. Intravenous heparin (3000 to 5000 U) was given during the procedure to all patients. Balloon inflation was assessed visually, and PTA was performed without using a manometer. Although dilation time was not monitored, it usually varied between 30 and 60 seconds in most patients. After PTA, the patients were randomly assigned to one of the following 4 EBR groups: 0 Gy (placebo), 7 Gy, 10.5 Gy, and 14 Gy, according to a table of random numbers. Envelopes containing the assigned groups were prepared in advance and were opened only after all eligibility criteria were met. The study was double-blinded, and the patients, interventional staff, and research nurses collecting the data were all unaware as to which group each patient belonged. Only the radiation oncology staff knew each patient’s group assignment. Patients in the placebo group (0 Gy) were managed in the same way (instructions, preparation, positioning, etc) as those in the other groups (7, 10.5, and 14 Gy) during the EBR session.

During PTA, the superior and inferior margins of the dilated vascular segment were identified under fluoroscopy with radioopaque markers on the skin. The sites of these markers were then identified on the skin with permanent ink. In the radiation oncology department, the treated leg was positioned in a Styrofoam cast customized for each patient. This cast kept the leg in the correct position during computer-assisted tomography (CT) planning, radiation simulation, and treatment. The patient then underwent a CT scan of the dilated segment of the femoropopliteal artery, with contrast medium injected through the introducer sheath. At the appropriate CT slices on a radiation treatment planning computer, the dilated vessel was then drawn. The computer then recreated the dilated vessel in 3 dimensions so as to treat only the target volume of tissue. The target to be treated was the dilated vessel along with a 2-cm radial margin and 3-cm inferior and superior margins. The target was treated in a single session. 24 hours after PTA, patients with 4 noncoplanar radiotherapy treatment fields with a 6-MV linear accelerator. Patients randomized to the placebo group underwent all steps, including being positioned on the linear accelerator, but no radiation was given.

The patients were referred from all 3 hospitals of our university medical center. However, all PTA and EBR administrations were performed in only one of these 3 hospitals because the EBR equipment was only available at that site. It was also easier to gather the research staff in the same hospital for logistic reasons.

**Follow-Up Evaluation**

The patients were followed up on an outpatient basis and were advised to walk regularly and to stop smoking. Glycoprotein IIb/IIIa receptor blockers and oral anticoagulation were not recommended, but aspirin was administered routinely to all patients after the procedure unless contraindicated. One year after PTA, all patients were asked to return for lower-limb angiography. Follow-up arteriography was performed earlier in patients with recurrent clinical symptoms considering severe enough to warrant reintervention. Patients subjected to arteriography for clinical reasons before the 12th month returned for another angiographic examination at 12 months if there was no definite arteriographic evidence of restenosis in the dilated segment. All patients were followed up in the clinic or contacted by telephone until recently.

**Quantitative Angiographic Measurements**

Angiograms were analyzed by an independent core laboratory (Montreal Heart Institute, Montreal, Canada) whose personnel were unaware of the radiation doses administered. All angiograms were analyzed quantitatively by experienced technicians, supervised by a cardiovascular radiologist, using edge-detection techniques with a computer-assisted method developed by Clinical Measurements Solutions (QCA-CMS version 5.2, Medis Imaging Systems). A centimetric radio-opaque ruler was placed on the tabletop for calculation of a correction factor to obtain absolute measurements in millimeters.

The computer automatically calculated the minimum lumen diameter, reference diameter, degree of stenosis (as a percentage of the diameter), stenosis length, and total length of balloon injury. In addition, 3-cm subsegments, proximal and distal to the dilated segment, were included to analyze the entire segment of the femoropopliteal artery subjected to EBR.

Lumen diameter and degree of stenosis (as a percentage of diameter) were measured on angiograms before PTA, immediately after PTA, and 12 months later or earlier in patients with recurrent symptoms considered severe enough to justify reintervention. Luminal loss was calculated as the difference between minimum lumen diameter immediately after PTA and that measured 12 months later. Restenosis was defined as a stenosis >50% of the lumen diameter within the dilated segment at follow-up. A first analysis was confined to the dilated vessel segment. A second analysis included the dilated vessel segment as well as the 3-cm proximal and distal margins. The proximal and distal margins, excluding the dilated segment, were also analyzed and reported separately.

**Statistical Analysis**

The sample size was based on the main study end point, which was the minimum lumen diameter within the dilated vessel segment 1 year after PTA. Given the cost of EBR and the risks associated with radiation therapy, we intended to detect a “large effect size” (effect size = 0.2 to 0.4). To have a power of 0.80 and a 2-tailed significance level of 0.05 to detect an effect size of 0.40 between the control group and one of the EBR groups, we calculated that 19 patients were required per group. To compensate for noncompliant patients and for those lost to follow-up, the sample size was increased to a total of 99 patients. The 4 groups of patients were compared in accordance with the intention-to-treat principle. For continuous variables, comparisons across the 4 groups were made by 1-way ANOVA. To take into account type I error, a global ANOVA comparing the 4 groups was first performed. Pairwise comparisons with the least-significant-difference procedure followed only if the global F test was significant at the 0.05 significance level. The study was not powered to detect differences between groups for baseline characteristics. However, for baseline characteristics that were related to the primary end point (minimum lumen diameter at follow-up) and that showed a potentially meaningful difference between groups, multivariable analyses were undertaken to make sure that these differences had no influence on the result. ANCOVA was used to adjust the comparison of the efficacy end point for relevant baseline characteristics. Categorical variables were analyzed with the χ² test. The statistical analyses were performed with SAS, version 8.2, and a 2-tailed significance level of 0.05 was used for all tests.
Results

The mean time intervals between PTA and radiation treatment were 23.49±0.70, 24.15±2.12, and 23.50±0.69 hours, respectively, in the 7-, 10.5-, and 14-Gy groups (P=0.159). The baseline demographic, clinical, and angiographic characteristics of the 99 patients enrolled in the trial are listed in Table 1. Three patients (3%) (1 patient in each of the 7-, 10.5-, and 14-Gy groups) died of unrelated causes before follow-up angiography. Five other patients (5%) (2 in the 10.5-Gy group and 3 in the 14-Gy group) declined to undergo follow-up angiography. The follow-up angiograms of 3 other patients (3%) (2 and 1 patients, respectively, in the 0- and 14-Gy groups) were not available for quantitative analysis. There were no quantitative angiographic analysis in the 0-, 7-, 10.5-, and 14-Gy groups, respectively.

Angiographic Analysis

Table 2 summarizes the data of the 88 patients with available quantitative angiographic analysis. Data at baseline and immediately after PTA were similar in all 4 groups. At follow-up, the minimum lumen diameter in the dilated vessel segments (the primary efficacy end point) was significantly larger in the 14-Gy group (2.91±1.32 mm) in comparison with the placebo group (1.92±1.22 mm, P=0.0072), the 7-Gy group (1.64±1.05 mm, P<0.001), and the 10.5-Gy group (1.92±0.95 mm, P=0.0071). The difference between the 14-Gy and placebo group was 0.98 mm, with a 95% confidence interval of 0.27 to 1.69 mm. Age, diabetes, hypertension, and clinical symptoms (claudication versus critical limb ischemia) before PTA were not associated (P>0.25) with minimum lumen diameter at follow-up. Multivariable analysis did not change the results when adjustments were made for sex, lesion length, and minimum lumen diameter after PTA (P=0.0039 without adjustment and P=0.0034 with adjustments). The reference diameter was strongly associated with minimum lumen diameter after PTA and, therefore, only the minimum lumen diameter after PTA was kept in the model because it had a stronger correlation with the primary criteria than the reference diameter. The difference remained significant when the dilated segment and margins were analyzed together (P=0.047 for 14-Gy versus the placebo group).

Luminal loss in millimeters was significantly smaller in the 14-Gy group in comparison with all other groups (P=0.0072 versus placebo, P=0.0028 versus 7 Gy, and P=0.012 versus 10.5 Gy). The cumulative frequency distribution of the loss of minimum lumen diameter of dilated vessel segments from immediately after angioplasty to follow-up at 1 year is shown in the Figure. The rates of restenosis of dilated segments were 50%, 65%, 48%, and 25%, respectively, in the 4 groups (P=0.072). These rates include 3 patients with diameter stenoses >50% (51% to 56%) immediately after PTA, as evaluated by quantitative angiography. These patients, 2 in the 14-Gy group and 1 in the 7-Gy group, were included in the analysis on the intention-to-treat principle. When data were excluded for these 3 patients with unsuccessful PTA from the analysis of restenosis, the difference in restenosis rates between the 14-Gy and placebo groups became significant (17% versus 50%, P=0.014). At follow-up, the reference diameter in the 14-Gy group was significantly larger than in the placebo group (4.81±1.37 versus 3.99±0.78 mm, P=0.0070). There was no significant difference in minimum lumen diameter and late luminal loss in millimeters in proximal and distal vessel segments irradiated but not dilated at baseline and at follow-up (Table 3). At follow-up, however, the reference diameters of these segments were significantly larger in the 14-Gy group than in the placebo group (P=0.012 for proximal segments and P<0.001 for distal segments).

Clinical Follow-Up and Side Effects

There were no major complications associated with PTA. Arteriography was performed ahead of time (<12 months
after PTA) because of recurrent clinical symptoms in 5 of 24 (21%), 5 of 24 (21%), 5 of 26 (19%), and 2 of 25 (8%) patients, respectively, in the 0-, 7-, 10.5-, and 14-Gy groups (P < 0.05). Reinterventions were performed in 6 of 24 (25%) patients in the placebo group (4 PTAs and 2 surgeries) versus 3 of 25 (12%) patients in the 14-Gy group (1 PTA and 2 surgeries) at 18 months’ follow-up (P < 0.24).

Among the 5 patients who declined follow-up angiography, 1 (10.5-Gy group) underwent surgical bypass at 7.4 months, 1 (14-Gy group) had recurrent claudication at the 30-month follow-up, and the others are symptom free, without additional intervention, at 2.5 to 5.0 years of clinical follow-up. One of the 3 patients whose angiograms were not available for quantitative analysis had repeated revascularization at 6 months (0-Gy group), and 2 others (1 in the 0-Gy and 1 in the 14-Gy group) had no reported restenosis on control angiograms.

Two patients in the 14-Gy group had transient thigh pain 2 to 4 months after EBR. The pain lasted a few months. In both patients, magnetic resonance imaging without gadolinium enhancement revealed a high muscle signal intensity on T2-weighted images, a nonspecific sign of tissue edema. In 1 patient, the muscle involvement extended well beyond the radiotherapy treatment field, making a causal relation to EBR unlikely. In the other patient, tissue edema corresponded to the treatment field and was possibly due to the radiation treatment. This patient reported the onset of mild activity-related thigh pain and swelling 3 months after the angioplasty. With a median follow-up of 4 years, no other side effects were observed.

**Discussion**

This study provides conclusive evidence that EBR at a dose of 14 Gy, given in a single session 24 hours after the procedure, reduces restenosis as demonstrated angiographically 1 year after PTA. In comparison with the placebo group, 14 Gy of EBR resulted in a 52% increase in minimum lumen diameter, an 88% decrease in luminal loss, and a 50%
Femoropopliteal restenosis is frequent and has been especially difficult to prevent. Stents have not been proven to decrease restenosis in femoropopliteal arteries, even when drug coated.1–6 Few controlled trials have been performed with brachytherapy in peripheral arterial obstructive disease.9,11–14 Although most of these studies reported a reduction of restenosis, a multicenter trial14 did not demonstrate significant benefit, whereas another found no difference in restenosis with the intention-to-treat analysis approach.13 The limitations of endovascular brachytherapy include the fact that it is sometimes technically impossible to deliver the radiation,13 that the required vascular manipulations are cumbersome, and that they may also be associated with thromboembolic events.15

The experience with EBR to prevent restenosis is limited. Observations on the effect of EBR in animals have been contradictory.16–21 In clinical studies, EBR did not prevent restenosis after PTA of hemodialysis fistulas22 or iliac or femoropopliteal arteries.23 EBR also had no significant effect on anastomotic intimal hyperplasia in prosthetic arteriovenous fistulas.24 However, the radiation dose fractions used in those studies (between 3 and 9 Gy) were probably too low and given too late to be effective. Brachytherapy trials have demonstrated a preventive effect against restenosis at doses of 12 Gy and higher.7–9 Lack of dose response with vascular radiation is not unexpected. Low-dose radiation to an injured vessel can even result in an increased restenosis rate, the so-called “edge effect,” or “candy-wrapper,” reported after either intravascular brachytherapy or radioactive stent implantation.25,26

EBR presents practical advantages over brachytherapy in limiting restenosis in extremity vessels. As demonstrated in this study, EBR does not need to be given at the time of intervention and is effective when administered 24 hours after PTA. Patients could therefore be referred to medical centers having EBR facilities after PTA. EBR does not interfere with the procedure and does not require large introducer sheaths, vessel-occluding centering devices, or additional vascular manipulations. EBR may be given on an ambulatory basis without irradiating the staff in the angiography suite and can be fractionated to deliver higher doses of radiation. It may be given despite tortuous anatomy and with very uniform and precise dosimetry, without being affected by lesion eccentricity or calcification. Hence, in larger and thickened atherosclerotic peripheral vessels, EBR allows adequate dosing of the adventitia without overdosing the intima.

Our study indicates that the effective dose of EBR to prevent restenosis after PTA is >10.5 Gy, when given as a single fraction. The effect of changing EBR timing, fractionating the dose, and increasing it to >14 Gy is now open to investigation. Although brachytherapy radiation doses >20

### Table 3. Quantitative Angiographic Results in Proximal and Distal Vessel Segments That Were Irradiated but Not Dilated*

<table>
<thead>
<tr>
<th>Variable</th>
<th>0 Gy  (n=22)</th>
<th>7 Gy  (n=23)</th>
<th>10.5 Gy (n=23)</th>
<th>14 Gy (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference diameter, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before angioplasty</td>
<td>4.36±0.74</td>
<td>4.49±0.77</td>
<td>4.34±0.80</td>
<td>4.67±1.15</td>
<td>0.68</td>
</tr>
<tr>
<td>At 12-month follow-up</td>
<td>4.18±0.93</td>
<td>4.28±0.75</td>
<td>4.12±0.85</td>
<td>4.97±1.29</td>
<td>0.023</td>
</tr>
<tr>
<td>Distal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before angioplasty</td>
<td>4.01±0.80</td>
<td>4.23±0.67</td>
<td>4.14±0.63</td>
<td>4.36±0.94</td>
<td>0.57</td>
</tr>
<tr>
<td>At 12-month follow-up</td>
<td>3.91±0.81</td>
<td>4.33±0.59</td>
<td>4.05±0.77</td>
<td>4.80±1.04</td>
<td>0.0046</td>
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<tr>
<td>Minimum lumen diameter, mm</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Before angioplasty</td>
<td>3.56±0.83</td>
<td>3.72±0.76</td>
<td>3.64±0.88</td>
<td>3.69±0.92</td>
<td>0.93</td>
</tr>
<tr>
<td>At 12-month follow-up</td>
<td>3.19±1.01</td>
<td>3.28±0.91</td>
<td>3.28±1.10</td>
<td>3.36±1.47</td>
<td>0.97</td>
</tr>
<tr>
<td>Distal</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Before angioplasty</td>
<td>3.10±0.97</td>
<td>3.51±0.65</td>
<td>3.39±0.71</td>
<td>3.51±1.29</td>
<td>0.46</td>
</tr>
<tr>
<td>At 12-month follow-up</td>
<td>3.05±1.25</td>
<td>3.32±1.01</td>
<td>3.30±0.77</td>
<td>3.55±1.15</td>
<td>0.52</td>
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<tr>
<td>Luminal loss, mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal</td>
<td>0.47±0.67</td>
<td>0.47±0.93</td>
<td>0.38±0.88</td>
<td>0.39±0.78</td>
<td>0.98</td>
</tr>
<tr>
<td>Distal</td>
<td>0.54±1.77</td>
<td>0.29±0.62</td>
<td>0.19±0.76</td>
<td>0.20±0.76</td>
<td>0.75</td>
</tr>
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</table>

*Plus-minus values are mean±SD.
Gy have been frequently administered to the intima without short-term side effects, such doses should be fractionated to be safely delivered with EBR. Decreasing the irradiated volume could also decrease or eliminate treatment side effects. This could be achieved with more recent methods of delivering EBR, such as intensity-modulated radiotherapy with linear accelerators and on-board cone-beam imaging. The use of EBR to limit interimal hyperplasia associated with stents in femoropopliteal arteries is another path to explore. Stent radio-opacity would also facilitate visualization of the target vessel. EBR could also be investigated to treat other vascular territories plagued with a high restenosis rate or in cases where the use of stents is less desirable, such as in hemodialysis fistulas.

The sample size of this study did not allow us to demonstrate statistically significant improvements in clinical outcomes. However, the reduction of restenosis observed in this study warrants pursuing larger trials with clinical end points and also justifies further investigations of EBR approaches and applications to prevent restenosis.

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References
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