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

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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=0.072).

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
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 \( \leq 0.9 \). 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 PTAs were performed under local anesthesia. Dilation diameter was chosen on the basis of the diameter of normal arterial segments. Intra-arterial 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 dilatation 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 radio-opaque 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 position constant between computed tomography (CT) planning, radiation simulation, and treatment. The patient then underwent a CT scan of the dilated segment of the femoropopliteal artery subjected to EBR. Lumen diameter and degree of stenosis (as a percentage of the 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. Lumen 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 \( \geq 0.40 \)). 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 \( \chi^2 \) 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. Therefore, 2 (8%), 1 (4%), 3 (12%), and 5 (20%) patients had no quantitative angiographic analysis in the 0-, 7-, 10.5-, and 14-Gy groups, respectively.

Table 1 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±2.22 mm, P=0.0028), 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 vascular 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 = 0.58). 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%
decrease in the proportion of dilated femoropopliteal artery segments with restenosis. The reduction in the binary restenosis rate reached statistical significance when patients with unsuccessful PTA (stenoses >50% immediately after PTA) were excluded. In addition, the reference vessel enlargement that occurred at follow-up in the 14-Gy group led to an underestimate of benefit when assessing the vessel lumen in comparison with the reference site.

Without histological or intravascular ultrasound data, it would be difficult to determine with certainty whether EBR prevents intimal hyperplasia or has a positive remodeling effect. However, EBR may have both effects. The increased reference diameter at follow-up in the 14-Gy group favors a positive remodeling effect. On the other hand, the very small late loss in the 14-Gy group favors a decrease in intimal hyperplasia because the atheromatous and calcified femoropopliteal lesions are unlikely to allow further expansion of the vessel lumen after PTA.

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.16–19 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>
</tr>
<tr>
<td>Minimum lumen 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>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>
<td></td>
<td></td>
<td></td>
</tr>
<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>
</tbody>
</table>

*Plus-minus values are mean±SD.
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 intimal 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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