Endovascular Brachytherapy for Prophylaxis of Restenosis After Femoropopliteal Angioplasty
Results of a Prospective Randomized Study

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Background—Inasmuch as endovascular brachytherapy (BT) has gained recent interest because of its inhibitory effect on mechanisms leading to restenosis after percutaneous transluminal angioplasty (PTA), we performed this randomized study to determine its efficacy for prophylaxis of restenosis after femoropopliteal PTA.

Methods and Results—One hundred thirteen patients (63 men, 50 women; mean age 71 years) with de novo or recurrent femoropopliteal lesions were included in this randomized trial comparing the restenosis rate after PTA plus BT (57 patients, PTA+BT group) versus PTA (56 patients, PTA group) without stent implantation. The mean treated length was 16.7 cm (PTA+BT group) versus 14.8 cm (PTA group). In patients randomized to PTA plus BT, a dose of 12 Gy was applied by an $^{192}$Ir source 3 mm from the source axis. Follow-up examinations included measurement of the ankle-brachial index, color-flow duplex sonography, and angiography. The primary end point of the study was patency after 6 months. The overall recurrence rate after 6 months was 15 (28.3%) of 53 in the PTA+BT group versus 29 (53.7%) of 54 in the PTA group ($\chi^2$ test, $P<0.05$). The cumulative patency rates at 12 months of follow-up were 63.6% in the PTA+BT group and 35.3% in the PTA group (log-rank test, $P<0.005$).

Conclusions—This is the first randomized study to demonstrate the efficacy of endovascular BT for prophylaxis of restenosis after femoropopliteal PTA. The value of this approach should now be improved by modification of the BT procedure and by combination with stent implantation. (Circulation. 2000;102:2694-2699.)

Key Words: peripheral vascular disease ■ angioplasty ■ restenosis ■ radioisotopes

Restenosis still remains a major limitation of the clinical usefulness of percutaneous transluminal angioplasty (PTA), and poor long-term results, especially after treatment of longer lesions in the femoropopliteal region, have been reported.1,2 Numerous pharmacological and mechanical adjuncts have been tried without success.

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The potential role of radiation in the prevention of restenosis after angioplasty has generated much recent interest. Ionizing radiation inhibits cellular proliferation and has been used extensively in the treatment of neoplastic and nonneoplastic diseases. The rationale in experimental studies to apply irradiation to prevent restenosis is that the latter is mediated at least in part by an uncontrolled proliferation of smooth muscle cells.3 Endovascular brachytherapy (BT) has shown strong potential in controlling this pathological proliferation process in animal models of restenosis.4 Findings of recent clinical studies suggest a substantial reduction in the restenosis rate with intraluminal irradiation of coronary5 and peripheral6 arteries in conjunction with angioplasty and stent implantation. In a recent pilot study,7 we demonstrated promising results concerning the possibility of reduction of restenosis by means of endovascular BT after long-segment femoropopliteal PTA without stent implantation. Therefore, we performed the present randomized study to determine the efficacy of endovascular BT for prophylaxis of restenosis after femoropopliteal PTA.

Methods

Patients

Each patient gave his or her written informed consent to participate in the study, which was approved by the hospital’s ethics committee.

Between November 1, 1996, and August 31, 1998, a total of 214 consecutive patients who were treated in our center with PTA for femoropopliteal lesions were screened for entry into the present study. To be eligible, the patients had to fulfill the following criteria: (1) minimum age of 40 years, (2) history of claudication (according to Rutherford stage 2 or 3)8 for ≥3 months or critical limb ischemia...
Baseline Characteristics of Patients According to Assigned Treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PTA (n=56)</th>
<th>PTA+BT (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female), n</td>
<td>34/22</td>
<td>29/28</td>
</tr>
<tr>
<td>Diabetes, n</td>
<td>29</td>
<td>26</td>
</tr>
<tr>
<td>Current cigarette smoker, n</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>Arterial hypertension, n</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>Cholesterol, mg/dL</td>
<td>245±44</td>
<td>238±51</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>159±38</td>
<td>147±44</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>174±74</td>
<td>190±150</td>
</tr>
<tr>
<td>Cardiovascular history (angina pectoris and/or prior myocardial infarction), n</td>
<td>20</td>
<td>26</td>
</tr>
<tr>
<td>Duration of symptoms, mo</td>
<td>6±5</td>
<td>6±6</td>
</tr>
<tr>
<td>Clinical stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Claudication (Rutherford 2/3), n</td>
<td>3/41</td>
<td>2/42</td>
</tr>
<tr>
<td>Rest pain ±tissue damage, n</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Lesion characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo, n</td>
<td>28</td>
<td>30</td>
</tr>
<tr>
<td>Recurrent, n</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Stenosis, n</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>Occlusion, n</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>Lesion length, cm</td>
<td>8.0±5.5</td>
<td>8.6±4.1</td>
</tr>
<tr>
<td>Treated length, cm</td>
<td>14.8±2</td>
<td>16.7±7.2</td>
</tr>
<tr>
<td>Runoff vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 to 1 patent artery, n</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>2 or 3 patent arteries, n</td>
<td>27</td>
<td>30</td>
</tr>
</tbody>
</table>

Continuous data are presented as mean±SD.

with pain at rest with or without tissue damage, (3) de novo lesion in the femoropopliteal region with a minimal lesion length of 5 cm or a recurrent lesion (after former PTA) of any length, (4) technical success of the angioplasty procedure that required angiological patency with residual stenosis of <30% diameter reduction, and (5) no further stent implantation. According to these criteria, 117 patients were included in the present study.

After successful PTA, the patients were randomly allocated to further BT or no further treatment. The patients were assigned to either group by adaptive randomization by using the following stratification criteria: (1) de novo lesion (≥5 cm) versus recurrent lesion (any length), (2) stenosis versus occlusion, and (3) clinical stage (claudication versus critical limb ischemia). Four of the 117 randomized patients were excluded from further follow-up (1 patient refused the BT procedure after randomization, and 3 patients, 2 in the PTA+BT group and 1 in the PTA group, had early recurrence within 24 hours). The baseline characteristics of the remaining 113 study patients (mean age 71 [43 to 89] years) with presenting symptoms, associated diseases and risk factors, and lesion characteristics are listed in the Table. The clinical stage of the patient’s disease was classified according to the categories defined by Rutherford and Becker. The mean length of the arterial segment treated by angioplasty was longer than the mean lesion length determined indication for PTA (see Table), because angioplasty also included segments with moderate stenoses in the adjacent proximal and distal region. Furthermore, in some patients, several stenotic lesions with short segments of a nearly normal vessel lumen in between were treated, and in these patients, PTA+BT was performed for the whole length, including the normal segments.

PTA and BT Procedures

An ipsilateral anterograde puncture and a 6F introducer sheath (Cordis Europe) were used in all procedures. Angioplasty was performed with 5- or 6-mm balloon catheters (Smash, Schneider Europe). The degree of residual stenosis immediately after PTA (or the degree of recurrent stenosis in case of follow-up arteriography) was determined by comparing the width of the contrast column (the measurements were made with a ruler) at the point of maximal diameter reduction within the dilated segment with that of an unaffected arterial segment immediately proximal to the dilated segment.

The region in which angioplasty was performed was marked with a radiopaque ruler, and movement of the table and angiographic unit was avoided to prevent parallax error. In patients randomized to further BT, the standard sheath was exchanged for a 55-cm 6F sheath (Brite Tip, Cordis Europe), which was advanced until its tip was 15 mm distal to the dilated segment. After placement of this sheath across the angioplastic site, a SF closed-tip noncentered applicator (Lumencath Applicator Nucletron, which accommodated the radiation source inserted during the afterloading procedure) was inserted and placed 15 mm distal to the dilated segment. This catheter was equipped with a wire with markers at 1.0-cm intervals for exact measurement of the length of the angioplastic site. The sheath and the applicator were fixed to the patient to prevent movement relative to the lesion during transportation to the brachytherapy unit. The position of the SF delivery catheter and the marked wire in relation to the target volume was verified by means of radiography before starting the afterloading procedure.

The BT procedure was performed by use of a remote high-dose-rate afterloading device as used in BT in general (micro Selectron, Nucletron). Treatment planning was performed with a computer-assisted standard dose calculation planning system (PLATO-BPS, version 13.2, Nucletron). A reference dose of 12 Gy was prescribed 3 mm from the source axis in the midplane of the applicator. (In case of ideal centering of the source in a vessel with a diameter of 5 mm, a dose of 15 Gy was calculated for the luminal surface, and a dose of 8 Gy was calculated for the adventitia. In case of centering, a minimum dose of 9 Gy and a maximum dose of 44 Gy were calculated to the luminal surface. The corresponding doses to the adventitia were 6 and 12 Gy, respectively.) The length of the artery to be irradiated corresponded to the total length of the angioplastic site with an additional 1 cm at each end, which has been chosen as a safety margin.

After the treatment planning, the proximal end of the applicator was connected by means of a special SF adapter to the afterloader. To ensure unimpeded placement of the active source, an inactive test wire (dummy wire) was placed. Then, an 192Ir source with a diameter of 1.1 mm and a mean activity of 200 GBq (150 to 366 GBq) was loaded. The mean irradiation time was 263 seconds (range 154 to 650 seconds).

Transportation to the BT unit and the irradiation protocol prolonged the PTA procedure by ~30 minutes (range 25 to 55 minutes). Treatment with 100 mg of aspirin per day was initiated at least 2 weeks before the intervention and was prescribed as long-term treatment. During the intervention, 5000 IU of standard heparin was administered, and further administration at a dosage of 1000 IU/h was started before transportation to the BT unit and was continued until the next morning.

Follow-Up

Follow-up examinations were performed the day after PTA and at 1, 3, 6, 12, 18, and 24 months after PTA. Follow-up examinations were assessment of symptoms, clinical examination, and noninvasive laboratory testing, including (1) ankle-brachial arterial pressure measurement with Doppler ultrasound to calculate the ankle-brachial pressure index (ABI) and (2) color duplex ultrasound (5-MHz linear-array color probe, model XP10, Acuson) of the femoropopliteal segment during each follow-up visit except for the visit at 1 month. The maximum peak systolic velocity in the dilated region was determined and compared with the peak systolic velocity in the preceding normal arterial segment. A focal increase in the peak systolic velocity of at least 140% (corresponding to a peak velocity ratio [PVR] of ≥2.4) was considered indicative of a stenosis of >50% at that site. If recurrent stenosis was suspected on the basis...
of clinical or laboratory findings (deterioration of the ABI by at least 0.15 from the maximum postprocedural level, a PVR in the dilated segment of at least 2.4, or both), intra-arterial angiography was performed with eventual further PTA. According to the high sensitivity of color duplex ultrasound for detection of $>50\%$ stenosis, control angiography was not mandatory in the case of normal hemodynamic results, but with patient consent, control angiography was also performed after at least 6 months in patients without suspicion of restenosis. Noninvasive laboratory testing, duplex ultrasound investigations, and angiographic follow-up investigations were performed and analyzed by investigators without knowledge of group randomization.

**Primary Patency**
The primary end point of the study was the patency of the recanalized segment after 6 months. Restenosis was defined as an angiographically verified stenosis of $>50\%$ narrowing of the luminal diameter within the recanalized segment compared with the diameters of normal segments of the vessel on the follow-up angiogram.

**Clinical Patency**
Clinical success of the procedure was defined by immediate improvement by at least 1 clinical category according to the criteria defined by Rutherford. Patients with tissue damage had to move up at least 2 categories and reach the level of claudication to be considered improved. Clinical patency is defined by sustained improvement without further intervention.

Target vessel revascularization was defined as further PTA or surgical bypass of the target vessel that was required because of the presence of $>50\%$ diameter stenosis of the target lesion.

**Statistical Analysis**
For data storage and statistical analysis, SAS software was used. The expected patency rate from PTA alone was, according to our own institutional experience and according to data in the literature, $\sim 20\%$ to $50\%$ for patients with long-segment or recurrent femoropopliteal lesions. Otherwise, according to data from our own pilot study and the experience of a German group, we could expect an absolute improvement of the primary patency rate of at least 20\% to 30\% by additional treatment with endovascular BT after angioplasty. We assumed that a 30\% absolute increase in restenosis rate is of important clinical relevance. To prove a 30\% absolute difference between these 2 treatment arms with a value of $P<0.05$ and a statistical power of 85\%, 82 patients had to be entered into the trial. To compensate for the dropout of patients lost to follow-up, we intended to include at least 100 patients. With proper patient enrollment, the inclusion of patients was to be stopped at the end of August 1998.

The Kaplan-Meier method was used to calculate the survival function, ie, the curve of the cumulative patency rate versus time. To test whether there was a statistically significant difference between survival curves ($P<0.05$), we used the log-rank test. The 6-month patency rates were compared between the groups by the $\chi^2$ test.

The time of recurrence was judged by recurrence of symptoms, or for patients with asymptomatic recurrence, the date of the regular planned control was taken as the failure date. Patients who died without known recurrence were censored with the date of their last control.

**Results**
The irradiation procedure was technically feasible in all patients without complications. The patients experienced no adverse events.

The follow-up period was 12±6 (mean±SD) months. Follow-up information by clinical examination and noninvasive laboratory testing (measurement of ABI and duplex sonography) could be obtained in 108 patients. Control angiography was performed in 69 patients (64\%), 37 in the PTA group and 32 in the PTA+BT group, after 9±5 months.

Five patients (4.4\%) were lost to follow-up after hospital discharge (1 in the PTA group and 4 in the PTA+BT group). In 1 of these 5 patients, information could be obtained about death without knowledge concerning patency of the recanalized segment.

**6-Month Patency**
In 107 patients, information concerning the patency of the recanalized segment could be obtained after 6 months (1 patient had died before the 6-month control).

The overall recurrence rate was 29 (53.7\%) of 54 in the PTA alone group versus 15 (28.3\%) of 53 in the PTA+BT group ($\chi^2$ test, $P<0.05$).

In the PTA group, 25 of 29 patients with recurrences presented with restenosis, and 4 of the 29 patients presented with reocclusion. Otherwise, in the PTA+BT group, none of the 15 patients with recurrence had reocclusion. An angiographic example for restenosis is given for each group in Figure 1 and Figure 2.

**Cumulative Patency**
The cumulative patency rates (Figure 3) of the recanalized segment, calculated by the Kaplan-Meier method, at 12 months of follow-up were 35.3\% in the PTA group and 63.6\% in the PTA+BT group (log-rank test, $P<0.005$).

**Hemodynamic Results**

**Ankle-Brachial Index**
The mean ABI increased from 0.50 (range 0.18 to 0.91) in the PTA group and 0.51 (range 0.1 to 0.92) in the PTA+BT group before PTA to 0.79 (range 0.40 to 1.13) and 0.85 (range 0.48 to 1.09), respectively, the day after PTA.

Follow-up examinations demonstrated mean values of 0.77 (range 0.15 to 1.14) and 0.88 (range 0.47 to 1.20) in the PTA
and PTA+BT groups, respectively, after 3 months and 0.74 (range 0.21 to 1.25) and 0.84 (range 0.27 to 1.25), respectively, after 6 months. (Values for patients with secondary interventions because of recurrence are not included.)

**Peak Velocity Ratio**

The mean PVR decreased from 7.3 (range 3.0 to 12.1) in the PTA group and 6.3 (range 2.7 to 11.9) in the PTA+BT group before PTA to 1.7 (range 1.05 to 2.2) and 1.7 (range 1.0 to 2.15), respectively, the day after PTA. The mean follow-up values were 2.50 (range 1.0 to 10.6) and 1.93 (range 1.0 to 11.8), respectively, after 3 months and 3.05 (range 1.1 to 9.8) and 2.41 (range 1.0 to 9.9), respectively, after 6 months. (Values for patients with secondary interventions because of recurrence are not included. Furthermore, in patients with occlusion, no PVR value can be calculated.)

Taking a cutoff value of ≥2.4 for the PVR to detect a >50% stenosis, we could demonstrate a sensitivity of 97% compared with angiography (see Figure 4).

**Clinical Patency**

The cumulative clinical patency rates (calculated by the Kaplan-Meier method) at 12 months of follow-up were 51.9% in the PTA group and 73.6% in the PTA+BT group, respectively (log-rank test, \( P < 0.05 \)).

**Reinterventions**

Target lesion revascularization was performed during a mean follow-up period of 12 months in 22 patients (in 20 patients by further PTA and in 2 patients by bypass surgery) in the PTA group and in 14 patients (all with PTA) in the PTA+BT group. None of the patients had clinical or hemodynamic deterioration because of progression of atherosclerosis at other sites of the treated leg. Otherwise, in 22 patients (9 in the PTA group and 13 in the PTA+BT group), angiography was primarily performed because of symptoms of the contralateral leg, and PTA in the contralateral leg was performed in 19 of these during the follow-up period.

**Complications**

The examination of the puncture site by means of duplex sonography the day after the intervention demonstrated a small pseudoaneurysm in 2 patients (1 in the PTA group and 1 in the PTA+BT group). Both were successfully treated by ultrasound-guided compression therapy. Two further patients (1 in each group) had hematoma at the puncture site with a drop in hemoglobin value between 2 and 3 g/dL.

Aneurysm formation was not observed in any patient by duplex sonography or angiography during a mean follow-up of 12 months. However, in 6 patients (1 in the PTA group and 5 in the PTA+BT group), a moderate ectasia (with a diameter of the vessel up to 9 mm) was observed in the treated segment.

**Survival**

During a mean follow-up of 12 months (range 6 to 24 months), 7 patients died (6.4% of the 109 patients with follow-up information concerning survival), 6 in the PTA
group and 1 in the PTA+BTr group. Five patients died from coronary heart disease, 1 died from stroke, and 1 died from cancer.

Discussion

A poor long-term patency rate after PTA of longer femoropopliteal lesions was repeatedly reported,12 and complex and longer areas of stenosis may have a 6-month patency rate as low as 23%.1 Restenosis constitutes the most important problem after successful angioplasty. Therefore, angioplasty is not generally accepted for treatment of longer femoropopliteal lesions by many vascular clinical specialists. The present study group consisted of patients at particular risk of restenosis because they had longer de novo lesions (≥5 cm) or because they had at least 1 previous episode of recurrence.

Extensive animal work1 and recently published findings of studies in humans5–9 have shown the feasibility of irradiation for the prevention of restenosis. Despite the use of different animal models, different arteries, and different isotopes with β or γ radiation, there is a remarkable consistency in the efficacy of endoluminal BT for inhibiting neointimal hyperplasia.

Although the classic concept of restenosis suggests migration and proliferation of smooth muscle cells from the media, results of recent experiments demonstrate that mainly myofibroblasts in the adventitia proliferate during the first days after angioplasty and may migrate into the intima.14 This has implications for the BT protocol, because it is important to know definitely the target tissue. At this time, the target tissue for radiation effects is not definitely known, and various dose prescription points and doses have been used in ongoing trials.15 In the present study, a reference dose of 12 Gy was prescribed at 3 mm from the source axis, which corresponds to the inner intimal layer of the vessel. This is in accordance with the study of Böttcher et al.16 This group has used a dose of 12 Gy because of the lengthy experience and positive results with this dose in the prevention of keloids. Unlike the present study, their study used postangioplasty irradiation only in segments with stents and shorter lesion lengths of 4.5 to 14 cm (mean 6.7 cm).6

The dose used in the present study was in the lower range compared with the dose used in most coronary trials using gamma sources.15 In the Scripps Coronary Radiation to Inhibit Intimal Proliferation Post Stenting (SCRIPPS) trial, which was a double-blind randomized trial comparing a noncentered 192Ir source with a placebo source after angioplasty of restenotic stented coronary lesions, a relationship between efficacy and minimum dose exposure was observed, inasmuch as an adequate treatment effect required that a minimum dose of at least 8 Gy be delivered to the entire circumference of the adventitial border.17

Despite the overall significant reduction of recurrence demonstrated in the present study, the remaining restenosis rate is still high because we could not prevent restenosis in about one third of our patients. As already mentioned, the dose used in our trial may not be adequate for complete inhibition of neointimal hyperplasia. Another important factor that can account for the observed restenoses in the present study may be the dose inhomogeneity due to an eccentric catheter position. Such poor centering of the source within the arterial lumen may result in areas of both relative underdosage and overdosage with respect to the prescribed dose. With long treatment lengths, a noncentered catheter can often be eccentrically located at various points along the vessel length. An eccentric plaque can further accentuate this noncentering.

In our experience, decentering of the source with the technique applied was not uncommon, although some centering may be achieved by the 5F radiation delivery catheter and the 6F sheath. Otherwise, source centering for γ emitters, such as 192Ir, is not as critical as it is for β emitters.18 New catheters with centering capabilities have been designed and are used in ongoing clinical trials. However, even if the source is perfectly centered, dose asymmetries will continue to result from eccentrically located plaques.

We did not observe an “edge effect” as reported in studies using BT after stent implantation or in studies with radioactive stents.19 This may be due to the use of a safety margin of 1 cm of irradiation surpassing the angioplasty length at each end.

There is anecdotal clinical evidence suggesting that radiation treatment may be associated with an increased rate of late thrombotic occlusion, which is due to delayed reendothelialization in balloon-injured irradiated vessels, particularly in newly stented vessels.20 This was not a problem in the present study, because in the case of recurrence, all patients in the BT group presented with restenosis, and no patient had thrombotic reocclusion.

Because there remains the question of whether radioactive therapy prevents the restenosis process or simply delays it, long-term studies are mandatory. Although short-term results have been promising, long-term efficacy and safety of this technique are not known. Recently, Teirstein et al21 reported in a small series that effectiveness of intracoronary BT was sustained over a 3-year period. Liermann et al22 also reported that the optimistic primary results have been confirmed by long-term results, with a range of follow-up of 4 to 68 months.

Limitations of the Present Study

The possible limitations according to dose (the prescribed reference dose may not be adequate for complete inhibition of neointimal hyperplasia) and to dose inhomogeneity (due to lack of a centering device) have been discussed above.

Control arteriography was not performed in every patient. However, color duplex sonography with measurement of the peak systolic velocity and calculation of the PVR is a very sensitive method for the detection of a reduction in luminal diameter of >50% in the femoropopliteal region. Ranke et al23 reported an optimal cutoff value of ≥2.4 for the PVR to detect an angiographically ≥50% stenosis, and we could demonstrate, by use of this cutoff value, a sensitivity of 97% to detect a >50% stenosis compared with angiography (see Figure 4).

We did not perform quantitative angiography, as used in coronary interventions, because this kind of evaluation of the angiograms was not used in peripheral interventions until recently.
The patients and the interventionists were not blinded to the treatment arm. However, to avoid bias at follow-up, noninvasive laboratory testing and angiographic follow-up investigations were performed and analyzed by investigators without knowledge of group randomization. The study was limited to a single center.

In summary, this is the first randomized study to demonstrate the efficacy of endovascular BT for prophylaxis of restenosis after femoropopliteal PTA. However, the results of our trial must be confirmed by a double-blinded randomized multi-institutional study using an adequate centering device before the use of endovascular BT can be generally recommended for prophylaxis of restenosis after femoropopliteal PTA.

References
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