Experimental therapeutic strategies in restenosis and critical limb ischemia

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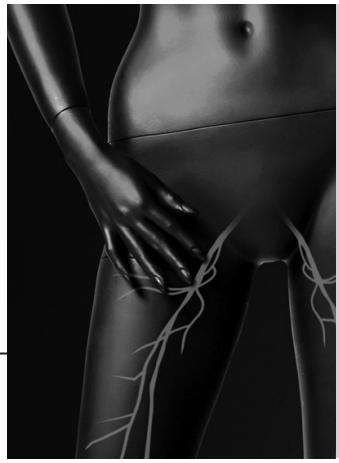

Chapter 04

External beam radiation therapy to prevent anastomotic intimal hyperplasia in prosthetic arteriovenous fistulas: results of a randomised trial

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Abstract

Background: The major cause for failure of prosthetic arteriovenous (AV) fistulas is caused by stenosis due to intimal hyperplasia at the venous anastomotic site.

Methods: Patients who were to undergo prosthetic AV fistula formation for hemodialysis were randomised to be treated with postoperative external beam irradiation (EBI) or surgery alone. In case of EBI, 18 Gray was applied at the site the venous anastomosis in two fractions. Primary end point was stenosis of the fistula after 12 months, as measured by duplex ultrasound. Secondary end point was failure of the fistula with the need for reintervention (primary patency).

Results: Fifty patients were randomly assigned to receive an 18 Gray postoperative dose in two fractions or to surgery alone. On an intention to treat base, the stenosis rate after 12 months by duplex ultrasound was 56% in the EBI group vs. 37% in the control group (log-rank test, $p = 0.58$). In the per protocol analysis, stenosis rates at the site of the venous anastomosis after 12 months were 66 and 37%, respectively (log-rank test, $p = 0.05$). The fraction of functioning AV fistulas without intervention after 1 year of follow-up was 36% in the EBI group and 51% in the control group (logrank test, $p = 0.29$). The per protocol analysis showed a 1-year primary patency rate was 20 and 54%, respectively (log-rank test, $p = 0.04$). In none of the patients were signs of any radiation related side effects.

Conclusion: Radiation treatment did not result in less stenoses or reinterventions after radiation in polytetrafluoroethylene dialysis access but might even worsen patency rates.

Introduction

A significant number of end-stage renal disease patients face chronic hemodialysis. With an estimated incidence of 150–200 individuals per million in the western population, maintenance of vascular access is of paramount importance in the care of these patients. Although an autologous radiocephalic fistula is the method of first choice, polytetrafluoroethylene (PTFE) grafts are frequently used because of failure or the impossibility to create an autologous fistula. Over 70% of the accesses placed in the United States are prosthetic grafts.[9] In The Netherlands, prosthetic grafts, mostly PTFE grafts, account for 30% of the access placements.[4]. The reported 1-year primary patency rate for prosthetic grafts of 35–45%, illustrates the susceptibility of this type of vascular access to develop complications.[5,7,9] The major cause for failure of prosthetic arteriovenous (AV) fistulas is thrombotic occlusion due to stenosis caused by intimal hyperplasia (IH). This stenosis preferably develops at the venous anastomotic site, or close by in the efferent vein.[14,17,27,29] The process of IH has not been completely unravelled yet. Maladaptive response to mechanical injury at surgery, compliance mismatch, high and/or low shear stress play a role.[2,3,6,15] Efforts to reduce IH focused on pharmacological agents have not been clinically successful.[11,13] Irradiation has been proposed as a method to prevent stenosis. Experimental studies have demonstrated its inhibiting effect on IH in animal models of restenosis.[1,12,19,22,25,32,34-37] Recent clinical data showed marked decrease of restenosis rate with endovascular brachytherapy after treatment of coronary and peripheral arteries.[18,20,23,28]

We performed a prospective, randomised trial in which the effect of external beam irradiation (EBI) on the survival of prosthetic AV fistulas was determined.

Methods

Patients

Between October 1998 and July 2001, patients who were considered for secondary access surgery or who had no suitable vessels for autologous AV access were included. The accrual was accomplished by two hospitals with a large dialysis population. The trial was approved by the medical ethical committee of the participating centers. Informed consent was obtained from each patient. Criteria for exclusion were: (1) complications during the operation; (2) history of radiation therapy at the site to be treated; (3) pregnancy; and (4) earlier randomization in the trial for a fistula in the same arm.

Randomization and data

Before surgery, patients were randomly allocated to external irradiation or no further treatment after placement of the prosthetic graft. The randomization was computer

generated using stratification within hospital. Block size was randomised between four and six. We used the telephone service of the trial office for the assignment of the treatment. Data were recorded and transferred to a database.

Treatment procedure

During surgery 6-mmPTFE (WLGore, Flagstaff,Arizona), AV fistulas were created between the brachial artery and the cephalic or basilic vein in either a loop or straight configuration. Three radio-opaque clips were placed to mark the venous anastomosis that is site deepest to the skin, at the proximal angle, and at the distal angle of the anastomosis. To locate the target for radiation therapy, AP- and lateral orthogonal X-ray films were taken in the radiation-oncology suite. Using a plastic mould, the supinated position of the forearm was similar to the position during radiation therapy. The clinical target volume was determined in a craniocaudal plane from 30 mm proximal (downstream) to the proximal clip to 10 mm distal (upstream) to the distal clip, and with a standard width of 2 cm. In case of EBI, 8–12 MeV electrons were applied; the dose was prescribed to the deepest part of the venous anastomotic site (clips). Field size was standardised to 5 x 6 cm. External irradiation in a dose of 18 Gy was delivered in two fractions of 9 Gy. The first dose of 9 Gy was given within 24 h after the operation, the second fraction of 9 Gy the next day. Patients in the EBI group who underwent surgery in the Hospital St. Franciscus Gasthuis, had to be transported to the Erasmus MC-Daniel den Hoed Cancer Center for the radiation therapy.

Follow-up

Follow-up examinations were planned after 3, 6 and 12 months. In addition to clinical examination, blood flow rates and duplex ultrasound (US) survey were performed (5-MHz linear-array colour probe). A stenosis was considered hemodynamically significant by duplex US if the peak systolic velocity (PSV) was .310 cm/s.[30,31] Flow measurements in the grafts were done by a US dilution technique (Transonic HD01 Hemodialysis Monitor; Transonic Systems, Inc., Ithaca, NY). Threshold for intervention were flow rates lower than 600 ml/min.[4] Angiography was performed on clinical indication. A stenosis was regarded significant on angiography if the vessel diameter was decreased to 50% or less.

End points and statistical methods

The primary end point was stenosis of the fistula after 12 months, as measured by duplex US. Secondary end point was failure of the fistula with the need for reintervention (primary patency).

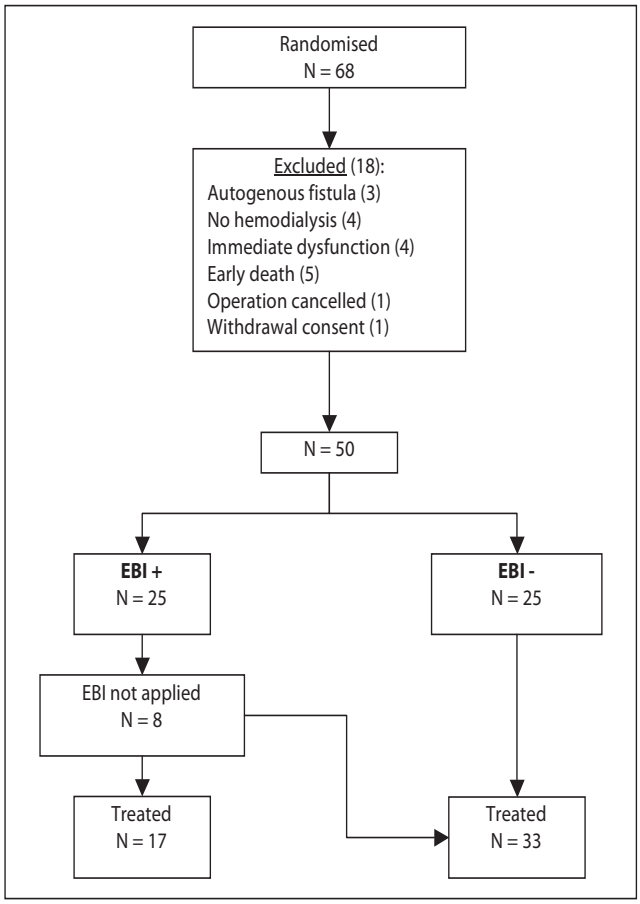
The Kaplan–Meier method was used to calculate the stenosis rate and the reintervention rate vs. time. To test whether there was a statistically significant difference between the curves (p<0:05), we used the log-rank test. The Fischer exact test was used to determine the effect of EBI and the use of antiplatelet therapy on the occurrence of thrombosis. With an assumed difference in stenosis rate after 12 months between the EBI group and the

control group of 30 and 60%, respectively, and a test power of 80%, a ¼ 0:05, each group required 48 patients. To adjust for exclusion after randomization, a total of 120 patients were planned.

Results

A total of 68 patients were enrolled in the study. We performed an interim analysis, also because of the disappointing accrual. Main reasons were the number of hospitals that were finally able to participate and overestimation of the amount of patients contributed by these centers. Eighteen patients were excluded after randomization for various reasons (Table 1). Of the 50 remaining patients who could be analyzed, 25 were men. The mean age was 59 years (range 19–85). Twenty-five of these 50 patients randomised for EBI.

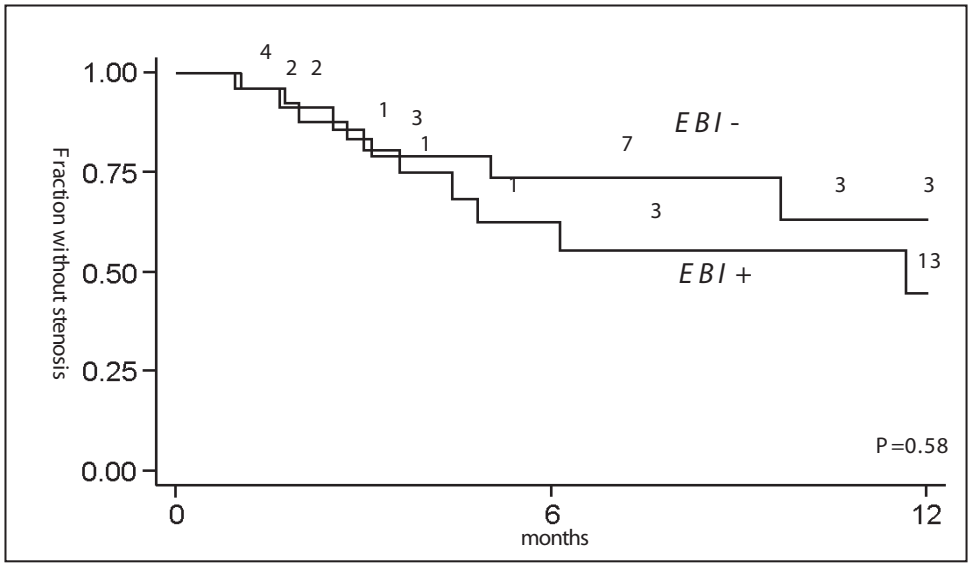
Table 1. *Flow diagram with number of randomised patients.*



Due to the described logistic factors of having surgery and radiotherapy in two different hospitals (six) and secondary patients' refusal (two), EBI was not applied in eight patients. Eight (16%) of the 50 patients died within the 1 year follow-up, most of them due to cardiovascular comorbidity. Two of them were treated in the EBI group. Furthermore, 26 patients underwent surgical or radiological reintervention because of thrombosis (four vs. three patients), stenosis (four vs. seven), infection (two vs. two), pseudoaneurysm at puncture site (two vs. zero), hemorrhage (one vs. zero) and seroma (zero vs. one), in the EBI and the control groups, respectively. Only one stenosis was found at the place of the arterial anastomosis, the rest was located at the venous site.

Three patients underwent kidney transplantation during the time of follow-up (after 5,9 and 12 months, respectively) and were considered off-study from that moment. No patients were lost to follow-up. Of the 50 patients, 41 were taking antiplatelet medication (carbasalatecalcium 100 mg), four had coumarines (acenocoumarol), and five had no such medication. In two of the five patients without any form of anticoagulant therapy, thrombosis occurred. In the other 45 patients, thrombosis happened five times. No significant difference was found (p=0.14, Fischer exact test). In the EBI group 4, thrombosed fistulas were observed (24%), vs. three occlusions (9%)in the control group (p=0.21, Fischer exact test). The interval in which thrombosis occurred varied from 30 to 218 days after fistula surgery. On an intention to treat base, the stenosis rate in the EBI group was 56% after 12 months vs. 37% in the control group (log-rank test, p=0.58). These results are shown in Fig. 1.

Figure 1. *Kaplan–Meier curves for fraction without stenosis in the EBI and control groups by intention to treat.*



In the per protocol analysis, stenosis rates at the site of the venous anastomosis after 12 months were 66 and 37%, respectively (log-rank test, p=0.05). The primary patency rate, i.e., the fraction without intervention of the AV fistulas after 1 year of follow-up was 36% in the EBI group and 51% in the control group (logrank test, p=0.29). The per protocol analysis showed a 1-year primary patency rate was 20 and 54%, respectively (log-rank test, p=0.04). In none of the patients were signs of any radiation related side effects.

Discussion

Radiotherapy has emerged as a promising technique to prevent restenosis. Clinical studies using endovascular beta- or gamma-radiation have shown its beneficial effect in addition to balloon angioplasty in coronary and femoral arteries.[18,20,23,28] AV fistulas, however, are pre-eminently suited for EBI because of their superficial locations. EBI is a non-invasive technique and gives a homogeneous dose distribution. Moreover, the dose can be fractionated. There is some evidence that the optimal time for irradiation is 1 or 2 days after the primary treatment.[25,35] Recently, Parikh and colleagues evaluated EBI in a feasibility study after angioplasty in patients with compromised AV fistulas; no short-term side effects were seen.[21] Cohen and co-workers found a minimal effect of EBI (reduction of restenosis) after angioplasty and stent placement in dialysis grafts.[8] Our study did not show a beneficial effect of EBI on stenosis after PTFE fistula surgery. In the patients treated per protocol, the results were even worse. Several possibly clarifying remarks for the negative results can be made. As in restenosis after angioplasty, with or without stenting, IH plays an important role after AV fistula surgery. However, there are some differences. In AV fistula, there is no pre-existing stenotic lesion, and the IH proceeds in a formerly normal venous segment. Moreover, the stimulus for IH is ongoing due to compliance mismatch and shear stress. Radiation doses of less than 15 Gy are unlikely to result in elimination of the restenosis problem but should only delay onset of restenosis.[16] The larger the dose, the more the delay.[10] The most conceivable idea is that the experimental observations reflect a situation in which the inhibition of restenosis is just delayed for the period of time necessary for the population of SMCs to regenerate, after which restenosis can occur as before. Some studies even suggest that EBI in a low dose (4 or 8 Gy) makes the restenosis problem worse.[24] A relatively large radiation dose seems necessary to permanently prevent restenosis. There are recent findings that a higher external beam dose (21 Gy or more) is mandatory.[16,33] A stereotactic technique should allow a high dose (21 Gy single fraction) to a relatively small volume encompassing the clips around the location of venous anastomosis. The fact that the reintervention rate due to thrombosis and stenosis in the treated group was higher might be associated with mainly experiencing the negative effect of EBI, i.e., delayed endothelial regeneration. This could be a justification for a longer period of antiplatelet therapy, though conflicting data exist with regard to its role in hemodialysis access failure.[26]

Major limitation of this study is that we did not realize the planned accrual. Furthermore, the number of noncomplying patients in our study was only partly foreseen. Logistic factors played an important role in the accrual. Treating physicians were not only vascular surgeons, but radiotherapists, nephrologists and radiologists as well. Planning of treatment turned out to be sometimes inaccurate due to mutual communication. Transferring patients to another center for radiation treatment entailed for an extra complicating factor. However, with these results it seems unlikely that a larger trial would have generated a different conclusion in favour of EBI.

Acknowledgements

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